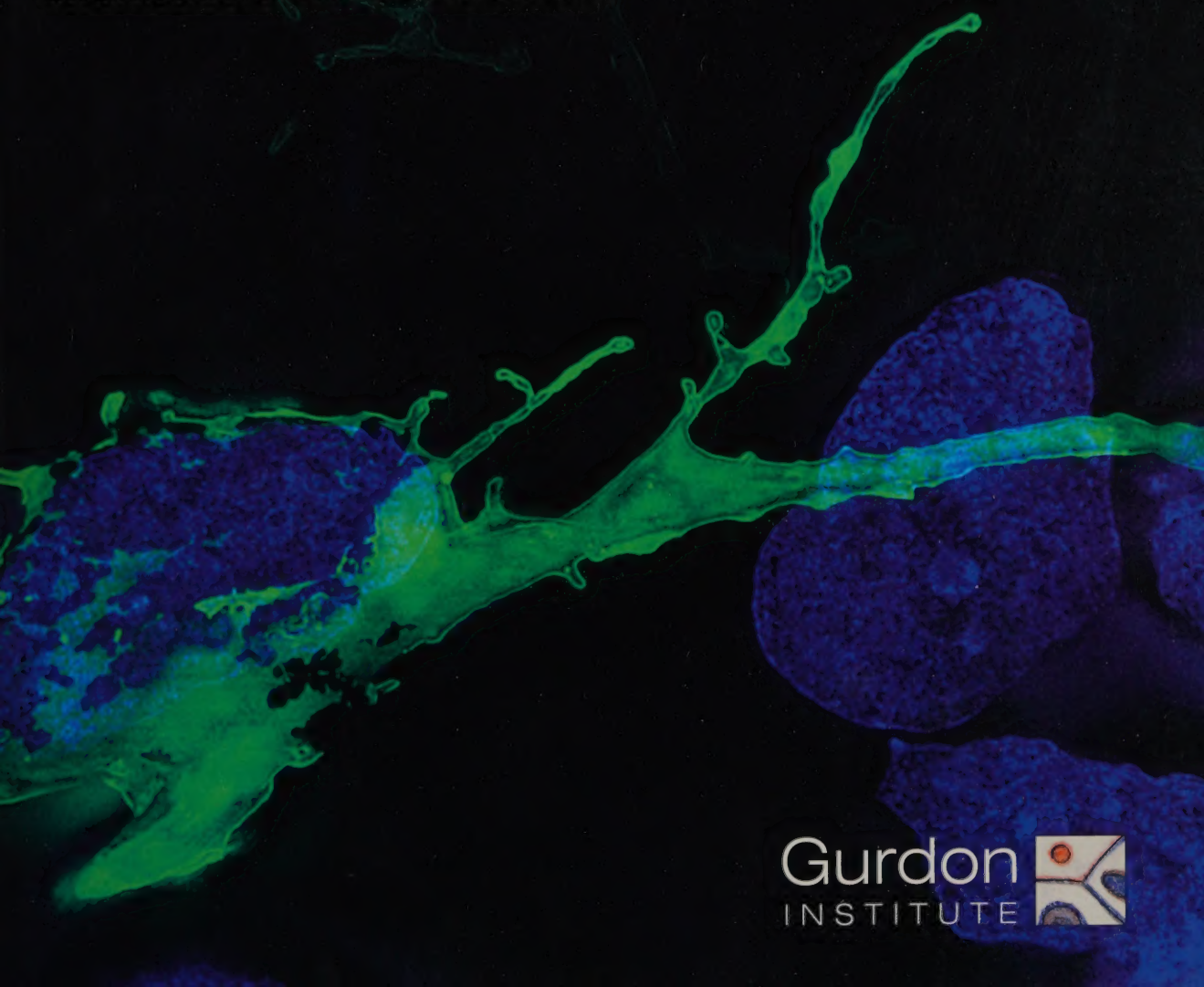


The Wellcome Trust/Cancer Research UK Gurdon Institute

2012 PROSPECTUS / ANNUAL REPORT 2011



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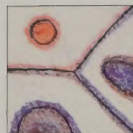
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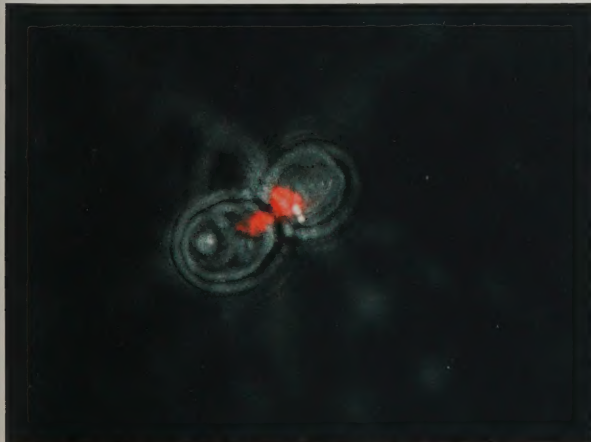
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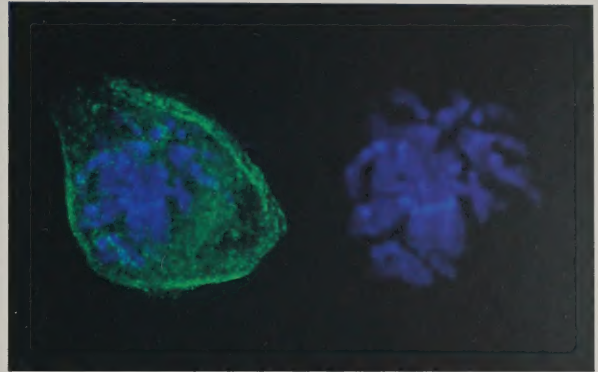
INTRODUCTION

As the reports from the individual research groups on the following pages demonstrate, 2011 has been another productive year for the Institute. The most notable changes have been the arrival of Dr Jenny Gallop as a new group leader, and the departure of Dr Masanori Mishima. Jenny joins us from Marc Kirschner's group at Harvard Medical School, where she developed an *in vitro* model for the formation of cellular protrusions, such as filopodia. She has been awarded a Wellcome Trust Research Career Development Fellowship and a European Research Council starting grant to study how membranes and actin regulators interact to control the assembly of various actin structures. Masanori is leaving us after six years in the Institute to become a Professor at the Centre for Mechanochemical Cell Biology that has just opened at the University of Warwick. We shall all miss him and his group very much, and wish them every success in their exciting new venture. We also said farewell to the staff of Mission Therapeutics, who had been provided space in the Institute for a year, while they set up their own laboratories. Mission Therapeutics is a new biotechnology company founded by Professor Steve Jackson to develop new anticancer treatments based on the work on DNA damage pathways coming out of his lab.

As usual, the outstanding research of my colleagues has been recognised by various prizes and awards. Steve Jackson was awarded



Separation of DNA (stained red with propidium iodide) between mother and daughter yeast cells. (Davide Mantiero & Vincent Gaggioli, Zegerman Group, 2011)



OMX photomicrograph of A dividing Primordial Germ cell (100x). GOF reporter, green; DAPI, blue. (Roopsha Sengupta, Surani Group, 2011)

the Royal Society's Buchanan Medal "in recognition of his distinguished contribution to medical sciences", as well as a European Research Council Advanced Investigator award to support his research into DNA damage responses. Tony Kouzarides has also been awarded a European Research Council Advanced Investigator grant to study the role of non-coding RNAs in transcription, and Azim Surani has won a Wellcome Trust Senior Investigator Award to study the principles and programming of the mammalian germline. Phil Zegerman was awarded the Cancer Research UK Hardiman Redon prize 2010. Many other groups in the Institute have also secured new research funding, bringing our annual income from grants to over £12 million this year.

Advanced imaging has always been one of the strengths of the Institute and 2011 has seen several important developments that will significantly improve our facilities in this area. For many years, the resolution of light microscopy was limited by diffraction, making it impossible to distinguish structures that are less than 200nm apart. A number of recent advances have now made it possible to resolve much smaller structures and the Institute has been awarded funding to invest in several systems that break the diffraction limit in different ways. Firstly, we have been awarded a Wellcome Trust equipment grant with other groups in Cambridge to purchase an OMX microscope that uses structured illumination to give twice the resolution of a standard light microscope. Secondly, Jenny Gallop has secured funding for a dSTORM (direct stochastic optical reconstruction microscopy) system that can resolve structures as small as 20nm, although it cannot image quickly. Finally, my group has been awarded a Wellcome Trust Strategic Award to collaborate with groups at Yale and Oxford Universities and the

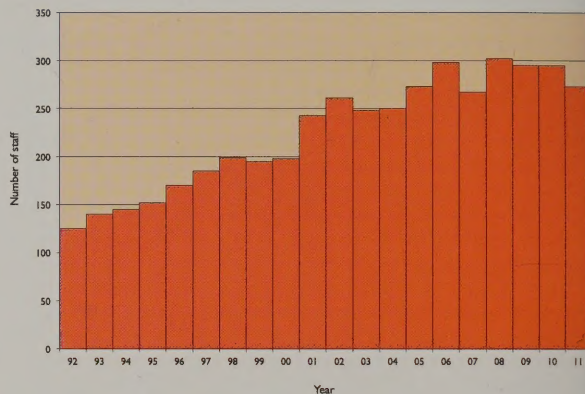
MRC Laboratory of Molecular Biology to develop the next generation of super-resolution microscopes that can image deep inside cells in real-time. Thus, the researchers in the Gurdon will be able to observe the behaviour of molecules in living tissues with unprecedented resolution, keeping us at the forefront of this rapidly moving field.

Much of the success of the Institute depends on its friendly and cooperative atmosphere, and I would like to highlight the role played by Gurdon Institute Postdoc Association in enhancing the scientific and social life of the Institute. This year, the postdocs hosted research seminars from Titia de Lange (Rockefeller University), Marco Foiani (IFOM-IEO, Milan) and Anne Ridley (King's College, London), as well as career talks by Jonathon Milner, a former Gurdon postdoc, now founder and CEO of Abcam, Pamela Feliciano, an associate editor of Nature Genetics, and Alison Schultdt who did her PhD in the Institute and is now chief editor of Nature Reviews Molecular Cell Biology. They also held a one day postdoc retreat that included a collaboration networking event, a session on how to supervise students and a barbecue. Most recently, the postdocs invited all of the core staff to a special beer and pizza 'Happy Hour' to thank them for all their work ensuring the smooth running of the Institute. I am therefore delighted to announce that the President of the Postdoc Association, Benjamin Klapholz, has been awarded this year's Martin Evans Memorial Cup, which is given annually to the person who has made the greatest contribution to the social life of the Institute.

Next year marks the 21st anniversary of the founding of the Gurdon Institute (although we only adopted this name in 2004), and we are busy preparing for a special symposium and celebration to mark our coming of age. We have lined up a distinguished list of participants, including three Nobel laureates, and half of the speakers will be former students and postdocs in the Institute who have gone on to become very successful group leaders elsewhere. If you are interested in joining us for what I am sure will be a very exciting meeting, details for how to register can be found at www.gurdon.cam.ac.uk/symposium/.

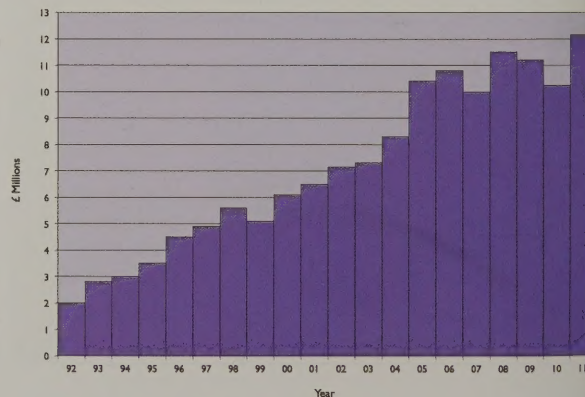
HISTORICAL BACKGROUND

The Institute was founded in 1989 to promote research in the areas of developmental biology and cancer biology, and is situated in the middle of the area containing the biological science departments of the University of Cambridge, close to the newly-established Wellcome Trust Institute for Stem Cell Research. The Institute hosts a number of independent research groups in a purpose-built building designed to promote as much interaction as possible. Developmental and cancer biology are complementary since developmental biology is concerned



Total number of staff 1992 - 2011

with how cells, including stem cells, acquire and maintain their normal function, whereas cancer is a result of a cell breaking loose from its correct controls and becoming abnormal. Both areas require a detailed knowledge of intra- and intercellular processes, which need to be analysed at the scientific and technical levels. To understand what goes wrong when a cell becomes cancerous requires knowledge of the processes that ensure correct function in normal development. At the technical level, the analysis of cellular and molecular processes requires familiarity with techniques that no single person can master; including



Total grant income 1992 - 2011

molecular biology, biochemistry, microarray technology, bioinformatics, cell culture, imaging and embryonic manipulations. There is, therefore, a major benefit in having scientists with different but complementary knowledge and technical skills working in close proximity to one another as is the case in the Institute.

The Institute is an integrated part of Cambridge University, and all group leaders are also members of another University department within the School of Biological Sciences, and contribute to both undergraduate and graduate student teaching.

CENTRAL SUPPORT SERVICES

The Institute's 'core staff' provides essential administrative, technical and computing support to our scientists so that the scientists can spend as much time as possible on their research.

FUNDING

Our two major funding bodies, the Wellcome Trust and Cancer Research UK continue to offer the Institute vital backing in the form of Fellowships, individual programme, project and equipment grants, in addition to our invaluable core funding.

Other sources of funding, both direct and indirect, include The European Commission, BBSRC, MRC, the Royal Society, NIH, the European Molecular Biology Organization, HFSP, the Isaac Newton Trust, the Association for International Cancer Research, the Alzheimer's Research Trust, the Federation of European Biochemical

Societies, the Japan Society for the Promotion of Science, the Sankyo Foundation of Life Science, the Swiss National Science Foundation, the Wenner-Gren Foundation, the Wiener-Anspach Foundation, the Cambridge Overseas Trust, Gates Cambridge Scholarships, DAAD, the Thai Government, the Liechtenstein Government, the Ramon Areces Foundation, Fundacao para a Gerência e Tecnológica, KAUST, March of Dimes, GSK and the Darwin Trust.

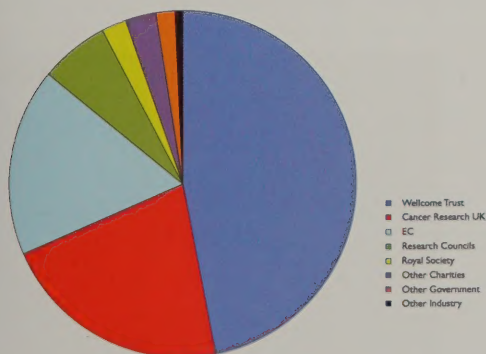
The University has also been very generous in its support of the Institute, particularly in funding equipment.

RETREAT

Our Annual Retreat this year was held at the Five Lakes Hotel, Maldon, Essex on 29th and 30th September 2011. The event was highly successful. Many Institute members attended and all gained from the experience both scientifically and socially.



The Institute on retreat, October 2011 (image by John Overton, Brown Group)



Grant sources (July 2010 - July 2011)

Professor Daniel St Johnston

Julie Ahringer

Chromatin regulation in transcription and splicing, and cell polarity establishment and transduction

Co-workers: Alex Appert, Dasha Ausiannikava, Ron Chen, Mike Chesney, Yan Dong, Bruno Fievet, Moritz Herrmann, Josana Rodriguez, Mariana Ruiz Velasco, Przemyslaw Stempor, Christine Turner, Eva Zeiser



Regulation of chromatin structure plays a central role in transcriptional control and also impacts mRNA post-transcriptional events. The small well-annotated genome, powerful RNAi technology, and rich resource of chromatin mutants of *C. elegans* make it an excellent system for studies of chromatin function. Through generation of a genome-wide map of 18 histone modifications in *C. elegans*, we found that many modifications are organised into broad chromosomal domains that differently mark the more recombinogenic distal arm regions and the central regions. We also found that exon and intron sequences are differentially marked by H3K36me3, and that H4K20me1 is enriched on the X chromosome and has a role in dosage compensation. We are studying the functions of different histone modifications in transcription and post-transcriptional processes such as mRNA splicing. We are also investigating the functions of *C. elegans* counterparts of major chromatin regulatory complexes that are implicated in human disease including the histone deacetylase complex NuRD, the Retinoblastoma complex DRM, and a TIP60 histone acetyltransferase complex. We study the function of these proteins in transcriptional control and development using chromatin immunoprecipitation followed by deep sequencing, global mRNA expression analyses and other genetic and genomic methods.

Cell polarity is crucial for many of the functions of animal cells, such as migration, axis formation, and asymmetric cell division. Many of the known molecules involved in cell polarity are conserved across animals, however, the mechanisms by which these function are not well understood. We use the one-celled *C. elegans* embryo to investigate the polarity cue, its reception, and how polarisation leads to downstream events such as asymmetric spindle positioning. We have completed a large number of genetic interaction RNAi screens that have identified many new cell polarity genes. We have

generated a large cell polarity network and are probing the functions of the new genes using a range of techniques, including live cell imaging, genetics, and biochemistry.

Selected publications:

- Cheung M-S, Down TA, Latorre I and Ahringer J (2011) Systematic bias in deep sequencing data and its correction by BEADS. *Nucleic Acids Research* 39(15):e103
- Zeiser E, Frøkjær-Jensen C, Jørgensen E and Ahringer J (2011) MosSCI and Gateway compatible plasmid toolkit for constitutive and inducible expression of transgenes in the *C. elegans* germline. *PlosOne* 6(5):e20082
- Liu T, Ahringer J et al (2011) Broad chromosomal domains of histone modification patterns in *C. elegans*. *Genome Research* 21: 227-236
- Gerstein MB, Ahringer J et al (2010) Integrative Analysis of the *Caenorhabditis elegans* Genome by the mod ENCODE Project. *Science* 330, 1775-87
- Kolasinska-Zwierz P, Down T, Latorre I, Liu T, Liu XS and Ahringer J (2009) Differential chromatin marking of introns and expressed exons by H3K36me3. *Nature Genetics* 41, 376-381



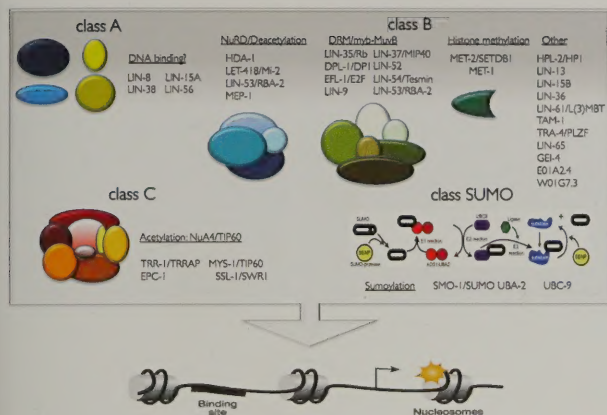


Figure 1 Many chromatin regulators under study are counterparts of proteins implicated in human disease.



Figure 2 Chromatin immunoprecipitation followed by high-throughput sequencing reveals common sites occupied by different chromatin regulatory complexes

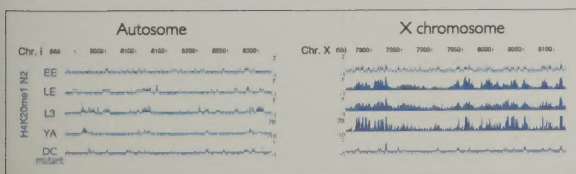


Figure 3 H4K20me1 has a role in X chromosome dosage compensation. ChIP tracks show enrichment on the X chromosome that is dependent on dosage compensation.

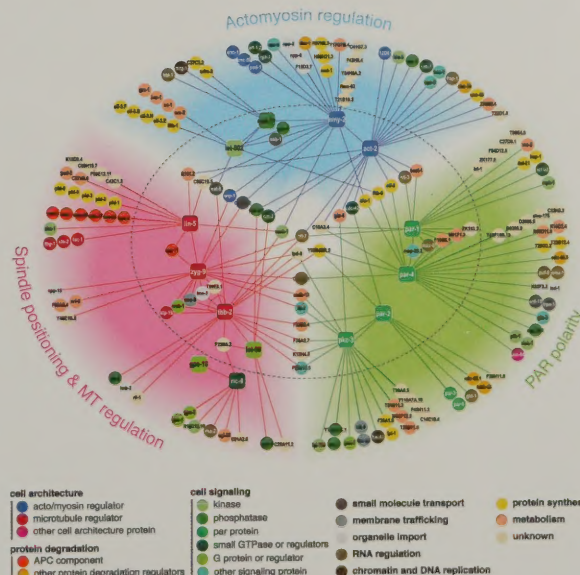


Figure 4 Interconnected cell polarity network derived from genetic interaction RNAi screening

Andrea Brand

Stem cells to synapses: regulation of self-renewal and differentiation in the nervous system

Co-workers: Janina Ander, Elizabeth Caygill, Esteban Contreras-Sepulveda, Melanie Cranston, Catherine Davidson, David Doupé, Jack Etheredge, Barret Pfeiffer, Katrina Gold, Jun Liu, Tony Southall, Pauline Spéder, Christine Turner



Discovering how stem cells are maintained in a multipotent state and how their progeny differentiate into distinct cellular fates is a key step in the therapeutic use of stem cells to repair tissues after damage or disease. We are investigating the genetic networks that regulate neural stem cells in *Drosophila*. Stem cells can divide symmetrically to expand the stem cell pool, or asymmetrically to self-renew and generate a daughter cell destined for differentiation. Symmetrically dividing stem cells exist in the optic lobe of the brain, where they convert to asymmetrically dividing neuroblasts. By comparing the transcriptional profiles of symmetrically and asymmetrically dividing stem cells, we identified Notch as a key regulator of the switch from symmetric to asymmetric division. The balance between symmetric and asymmetric division is critical for the generation and repair of tissues, as unregulated stem cell division results in tumorous overgrowth.

During asymmetric division cell fate determinants, such as the transcription factor Prospero, are partitioned from the neural stem cell to its daughter. We showed that Prospero acts as a binary switch between self-renewal and differentiation. By identifying Prospero's targets throughout the genome we showed that Prospero represses genes for self-renewal and activates differentiation genes. In Prospero mutants, differentiating daughters revert to a stem-cell-like fate: they express markers of self-renewal, continue to proliferate, fail to differentiate and generate tumours.

Neural stem cells transit through a period of quiescence at the end of embryogenesis. We showed that insulin signalling is necessary for these stem cells to exit quiescence and reinitiate cell proliferation, we identified nutrition-responsive glial cells as the source of the insulin-like peptides that reactivate neural stem cells *in vivo*.

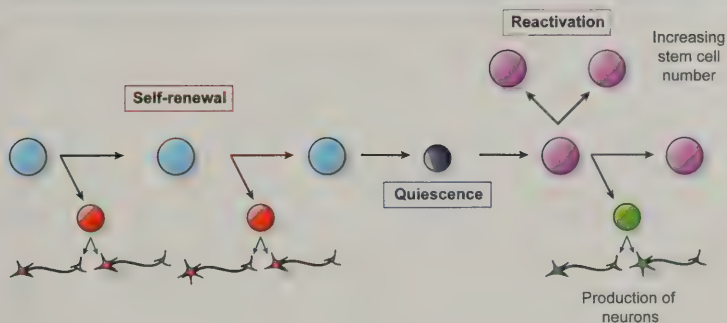
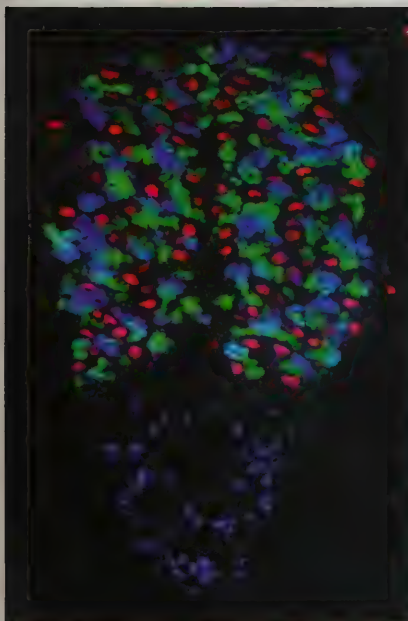
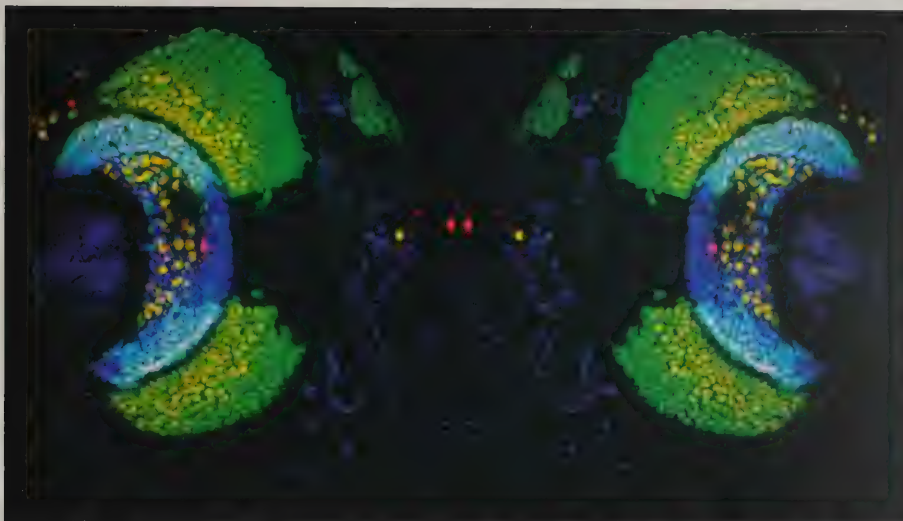
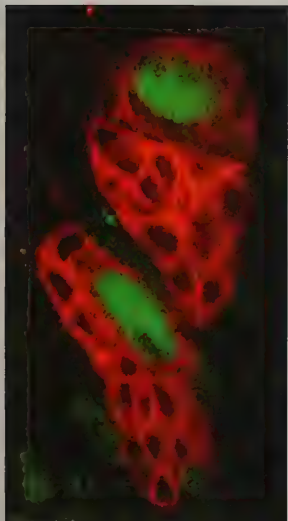
For more information, see the Brand lab home page:

<http://www.gurdon.cam.ac.uk/~brandlab/>

Selected publications:

- Chell JM and Brand AH (2010) Nutrition-responsive glia control exit of neural stem cells from quiescence. *Cell* 143(7), 1161-1173
- Egger B, Gold KS and Brand AH (2010) Notch regulates the switch between symmetric and asymmetric neural stem cell division in the *Drosophila* optic lobe. *Development*, 137, 2981-2987
- Bardin AJ, Perdigoto CN, Southall TD, Brand AH and Schweisguth F (2010) Transcriptional control of stem cell maintenance in the *Drosophila* intestine. *Development* 137, 705-714
- Monier B, Pellissier A, Brand AH and Sanson B (2010) An actomyosin-based barrier inhibits cell mixing at compartmental boundaries in *Drosophila* embryos. *Nature Cell Biology* 12, 60-65
- Southall TD and Brand AH (2009) Multiple transcription factor binding identifies neural stem cell gene regulatory networks. *EMBO J.* 28, 3799-807





Top left: two neural stem cell clones in the larval brain, labelled in red. Neuroblast nuclei are green

Top right: Lineage tracing in the *Drosophila* optic lobes of the *Drosophila* brain, using the *Grave* system. Cells currently expressing the transcription factor *Optix* express RFP (red); cells descended from *Optix*-expressing cells express GFP (green). The transcription factor *Dachshund* (blue) marks the lamina region of the developing visual system.

Left: Expression of temporal transcription factors *Castor* (green) and *Chinmo* (blue) in the larval ventral nerve cord. Neuroblasts in red.

Above: *Drosophila* neural stem cells (blue) divide asymmetrically during embryogenesis, to self-renew and generate differentiating daughter cells (red). Neural stem cells then enter a period of quiescence (grey) from which they are reactivated to expand the stem cell pool (purple) and generate the neurons of the adult nervous system (green).

Nick Brown

Molecular analysis of morphogenesis

Co-workers: Natalia Bulgakova, Jonathan Friedlander, Anabel Griffiths, Sven Huelsmann, Yoshiko Inoue, Benjamin Klapholz, John Overton, Nikki Parsons, Peerapat Thongnuek



Cellular adhesion and communication are vital during the development of multicellular organisms. These processes use proteins on the surface of cells, receptors, which stick cells together (adhesion) and/or transmit signals from outside the cell to the interior, so that the cell can respond to its environment. Our research is currently focused on how adhesion receptors are linked with the cytoskeleton to specify cell shape and movement within the developing animal. This linkage between the adhesion receptors and the major cytoskeletal filaments contains many components, giving it the ability to grow or shrink in response to numerous signals. For example, as the cytoskeleton becomes contractile and exerts stronger force on the adhesion sites, additional linker proteins are recruited in to strengthen adhesion.

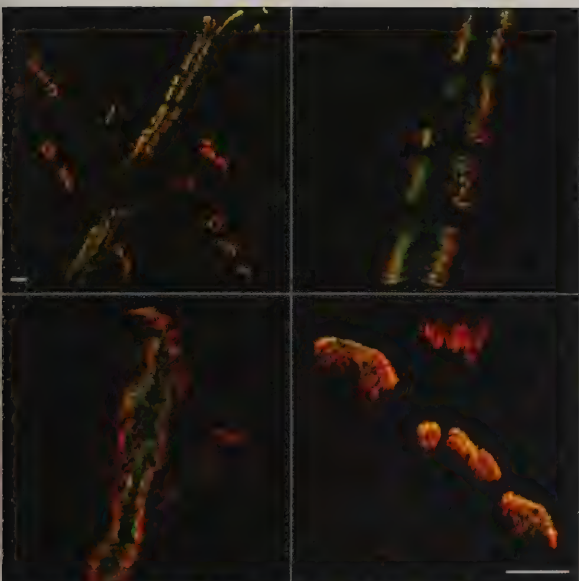
We use the fruit fly *Drosophila* as our model organism to discover how the complex machinery linking cell adhesion to the cytoskeleton works, and contributes to morphogenesis. We are seeking to discover how adhesion receptors form contacts of differing strength and longevity, at one point mediating dynamic attachments as the cell moves, and at another point stable connections essential for the functional architecture of the body. At these stable sites of adhesion, such as the integrin-dependent attachments of the muscles, we can see that the different components have unique properties and distribution (Fig 1). By combining quantitative imaging with genetics we are discovering the rules that govern the assembly of the integrin adhesion complex. To combine biophysical approaches with genetics, we are establishing muscle attachments in culture (Fig 2). We find that the other major cytoskeletal element, microtubules, regulates both integrin and cadherin adhesion (Fig 3). Another important question is how a variety of actin-membrane linkages are formed in the same cell, which can be addressed particularly well in the developing egg chamber. There is a rapid change in the actin structures in nurse cells, with

new synthesis of cytoplasmic actin cables from the plasma membrane, extending inwards to connect to an actin network surrounding the nucleus (Fig 4). We are currently addressing how the different actin structures in the cell are coordinated by actin-binding proteins, such as adducin and spectraplaklin.

Selected publications:

- Brown NH (2011) Extracellular matrix in development: insights from mechanisms conserved between invertebrates and vertebrates. **Cold Spring Harb Perspect Biol** E-pub ahead of print
- Zervas CG, Psarra E, Williams V, Solomon E, Vakaloglou KM and Brown NH (2011) Central multifunctional role of Integrin-Linked Kinase at muscle attachment sites **J Cell Sci** 124, 1316-1327
- Delon I and Brown NH (2009) The integrin adhesion complex changes its composition and function during morphogenesis of an epithelium. **J Cell Sci** 122, 4363-4374
- Delon I and Brown NH (2007) Integrins and the actin cytoskeleton. **Curr Opin Cell Biol** 19, 43-50





*Fig 1: Different views of muscle attachment sites from *Drosophila* embryos, showing the distribution of two proteins that link integrin extracellular matrix receptors to the cytoskeleton (Git in green and integrin-linked-kinase in red). Note that they are in distinct regions of the attachment structure, suggesting that the two proteins have different roles.*

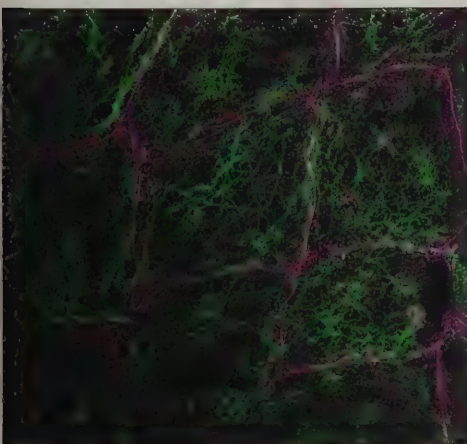


Fig 3: Arrays of microtubules (green) in the amnioserosa cells regulate the cell-cell adhesion molecule cadherin (magenta)

Fig 2: Primary cell culture of embryonic muscles, showing integrin adhesions (green) connected to actin filaments (red).

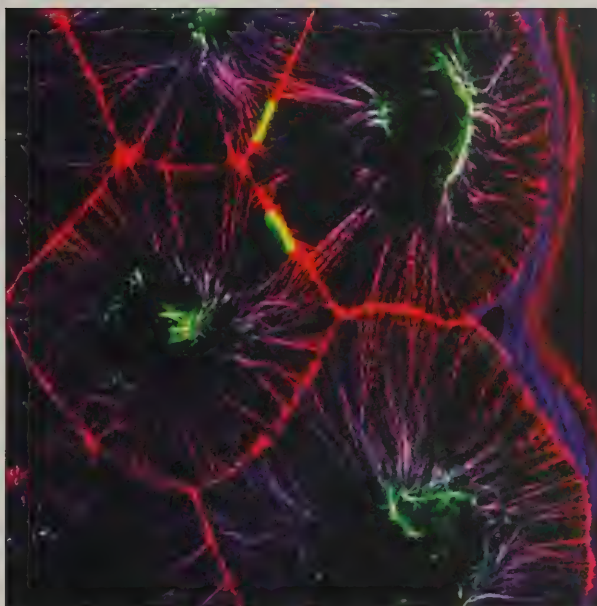
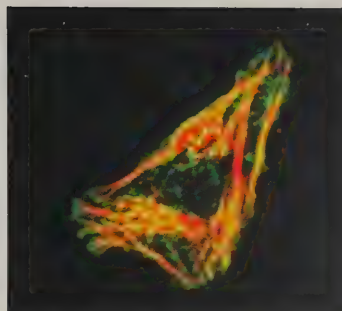


Fig 4: Actin cables (red) extending from the plasma membrane to the nucleus (visible as black area in the centre of each cell) in nurse cells hold the nucleus in place during dumping. The spectraplaklin Short stop (blue) is enriched on the parts of the actin cables close to the nucleus (red and blue = magenta), where they connect to an actin meshwork surrounding the nucleus, containing the actin-networking protein adducin (green).

Rafael Carazo Salas

Functional genomics of cell morphogenesis

Co-workers: Juan Francisco Abenza Martinez, Anatole Chessel, James Dodgson, Marco Geymonat, Veronika Graml, Jonathan Lawson, Yung-Chin Oei, Kathy Oswald, Claudia Stocker, Xenia Studera



An extraordinary capacity of cells is their ability to modulate their shape, polarity and intracellular cytoskeletal organisation, according to the functions they need to perform. Our work seeks to identify the gene and protein networks that regulate these three processes and overall cell morphogenesis, in space and time. To that end we adopt a multi-disciplinary approach combining high-content and quantitative microscopy, genetics, biochemistry and computational methods. We use fission yeast as our primary model organism and plan to extend our scope to mammalian cells in the future.

We recently established a high-throughput/high-content microscopy platform for yeast-based functional genomics studies. Using that platform and systematic gene knock-outs, we recently completed the first comprehensive live cell-based screen for microtubule and cell shape regulators and discovered tens of potential novel regulators that we are in the course of validating. With that screen, we hope to obtain the most exhaustive genomic map and spatiotemporal annotation of such regulators to date. Various other microscopy-based functional genomics projects are also ongoing in our group.

We have also developed, in collaboration with theoreticians, computational methods to simulate the collective interaction of microtubules and microtubule regulator recipes in 3D over time, in order to clarify the mechanisms that precisely pattern microtubules in cells. We find that, together with regulator abundance, cell geometry is a strong determinant of microtubule pattern, something we are actively investigating experimentally.

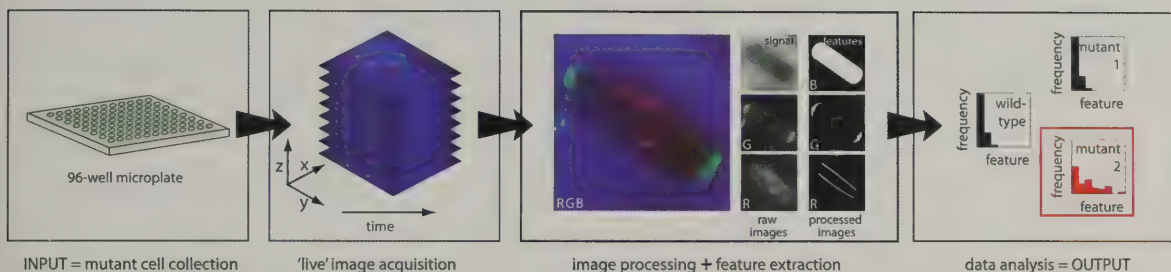
Lastly, we have begun characterising the dynamics and structure of the polarity machinery at high spatiotemporal resolution. Using live super-resolution microscopy and custom-made image analysis tools, we find that components of the machinery previously thought to regulate polarity by physically interacting at the cell cortex actually localise to separate, distinct complexes. This

suggests novel layers of polarity regulation we are seeking to unravel.

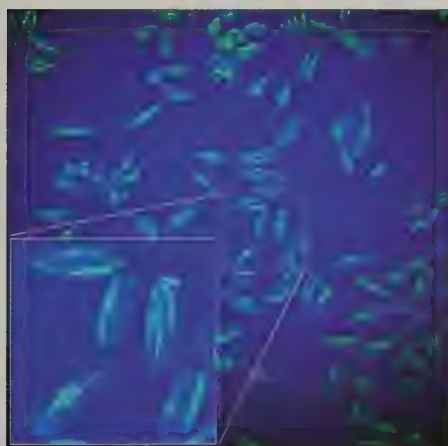
Selected publications:

- **Carazo-Salas RE**, and Nurse P (2007). Sorting out interphase microtubules. *Mol Syst Biol* 3:95-6.
- Salinas S, **Carazo-Salas RE**, Proukakakis C, Schiavo G, Warner TT (2007). Spastin and microtubules: Functions in health and disease. *J Neurosci Res* 85(12):2778-82.
- **Carazo-Salas RE**, and Nurse P (2006). Self-organization of interphase microtubule arrays in fission yeast. *Nat Cell Biol* 8(10):1102-7.
- Salinas S, **Carazo-Salas RE**, Proukakakis C, Cooper JM, Weston AE, Schiavo G, Warner TT (2005). Human spastin has multiple microtubule-related functions. *J Neurochem* 95(5):1411-20.
- **Carazo-Salas RE**, Antony C, Nurse P (2005). The kinesin Klp2 mediates polarization of interphase microtubules in fission yeast. *Science* 309(5732):297-300.



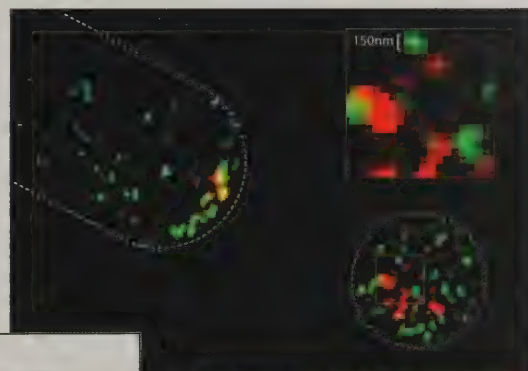
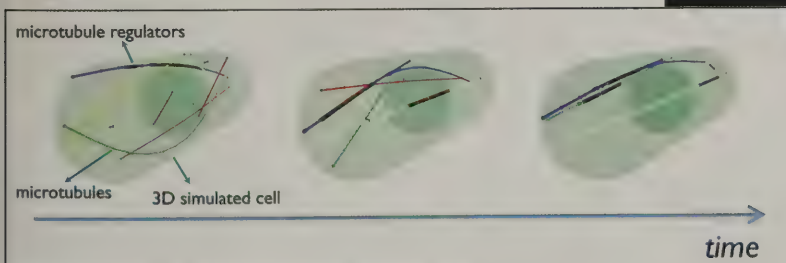


A high-throughput/high-content microscopy workflow used to systematically screen through the genome for novel regulators of cell morphogenesis.



High-resolution image of cells expressing GFP-tubulin, generated with an automated high-throughput spinning disc confocal microscope.

Snapshots from a computer simulation of microtubule organisation in a virtual cell.



Polarity complexes visualised at superresolution. Live cells expressing two fluorescently-labelled (green:GFP, red:mCherry) polarity factors. Superresolution reveals that both factors, thought to regulate polarity by physically interacting, belong to separate 150nm-sized complexes. Left: cell visualised 'sideways'. Right: cell visualised 'head on'. Dotted lines: cell contours.

Thomas Down

Epigenomics and transcription informatics

Co-workers: Paulina Chilarska, Kenneth Evans, Jing Su



We study the mechanisms by which programs of gene expression are selected and perpetuated during the development of multicellular organisms. Regulatory sequence elements contain clusters of binding sites for transcription factors, most of which interact with some specific DNA sequence motif. By discovering the repertoire of transcription factor binding sites, we can uncover an important part of the cell's regulatory network. We are addressing this question using a new computational motif discovery tool, NestedMICA, to find DNA sequence motifs that are over-represented in larger sets of regulatory sequences from across the genomes of a panel of multicellular organisms.

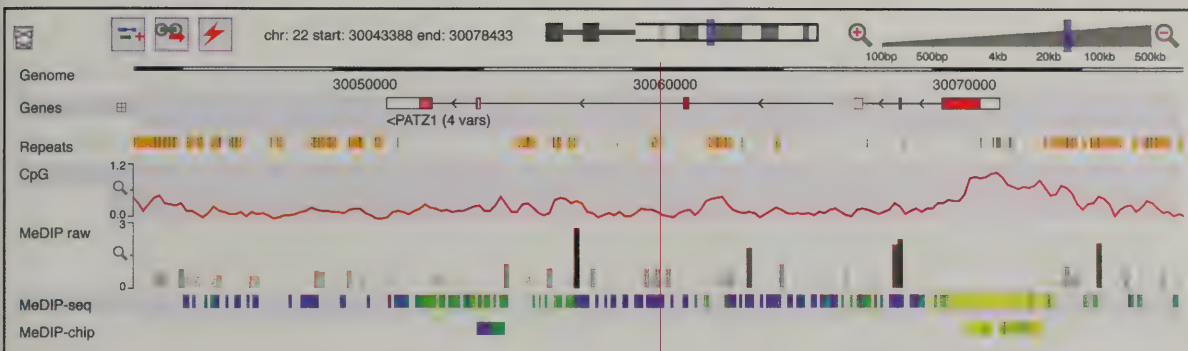
It has become increasingly clear that the function of regulatory elements depends on their context in terms of nuclear location and chromatin structure. To this end, we are keen to understand the landscape and functions of stable epigenetic modifications - particularly DNA cytosine methylation. High-throughput sequencing technologies allow epigenetic marks to be studied on a genome-wide basis, and we have used a combination of deep sequencing and a new analytical technique to generate the first map of DNA methylation across a complete vertebrate genome. We are now combining this technology with other analysis and data visualisation methods in order to study how DNA methylation interacts with other regulatory and epigenetic mechanisms. We are also investigating how human DNA methylation changes are associated with ageing and complex diseases.

Selected publications:

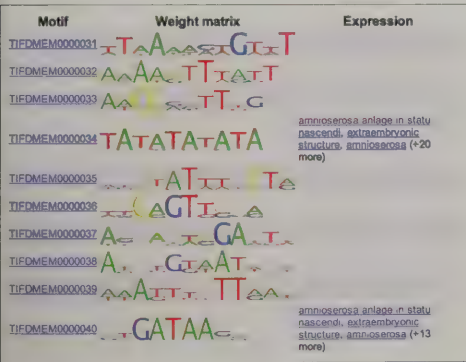
- Rakyan VK, **Down TA**, Maslau S, Andrew T, Yang T-P, Beyan H, Whittaker P, McCann OT, Finer S, Valdes AM, Leslie RD, Deloukas P, and Spector TD (2010) Human aging-associated DNA hypermethylation occurs preferentially at bivalent chromatin domains. **Genome Res** 20:434-439

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- **Down TA**, Bergman CM, Su J and Hubbard TJP (2007) Large scale discovery of promoter motifs in *Drosophila melanogaster*. **PLoS Comput Biol** 3:e7
- **Down TA** and Hubbard TJP (2005) NestedMICA: sensitive inference of over-represented motifs in nucleic acid sequences. **Nucleic Acids Res** 33, 1445-1453

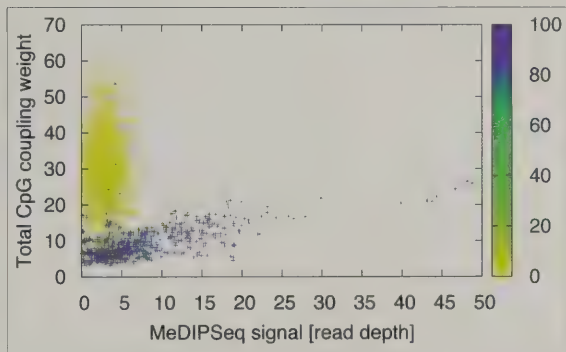




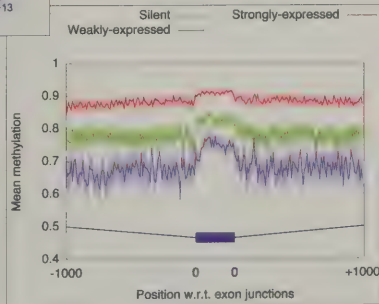
Methyl-DNA immunoprecipitation (MeDIP-seq) data before and after normalisation using the Batman method. Viewed in the Dalliace genome visualisation tool (<http://www.biodalliance.org/>)



The BioTIFFIN interface for browsing regulatory sequence motifs.



The Methyl DNA Immunoprecipitation (MeDIP) technique can be used to quantify the methylation state of genomic DNA on a large scale. In methylated regions (coloured blue), signal correlates with the density of CpG dinucleotides.



Multiple epigenetic marks "paint" exons in the genome. In the case of DNA methylation (shown here) the marking of exon boundaries is remarkably sharp, and appears to be independent of transcription. (single-base methylation data from Lister et al, Nature AOP 14th October 2009).

Jenny Gallop

Membranes, actin and morphogenesis

Co-workers: Lynn Froggett, Julia Mason



Understanding the molecular basis of cell shape and the changes that occur when cells move is vital for understanding the different cell rearrangements that underlie morphogenesis. The actin cytoskeleton is of key importance. The actin cytoskeleton is remodelled in response to changes in the cellular environment, which are transduced through signalling at the plasma membrane. Many actin regulators are recruited to membranes and my lab will study how the organisation of proteins at membranes prompts the formation of distinct actin structures that influence cell shape and movement. We hope to gain a better understanding of how the changes in cell shape lead to morphogenesis in the whole organism.

We will particularly concentrate on how actin is polymerised during filopodia formation and endocytosis. Filopodia are finger-like actin-rich protrusions that are thought to be sensory structures. In previous work I established an *in vitro* reconstitution system using supported lipid bilayers and *Xenopus* egg extracts that recapitulates the formation of actin structures resembling filopodia (Fig 1), and proposed a model for how filopodia form in cells (Fig 2). The role of actin in endocytosis is somewhat unclear, but there are many molecular links that suggest it is important. Endocytic actin structures can also be recapitulated using reconstitution systems and key actin regulator, *toca*, found using this approach, appears to be involved in endocytosis and gastrulation in *Xenopus* (Fig 3).

Specifically we will ask: how are filopodia formed? How are endocytic actin structures generated at the membrane and in what ways is this different from filopodia formation? How are the proteins that regulate actin structures used during morphogenesis? To answer these questions we will take a two-pronged approach: (1) reconstitution of actin polymerisation *in vitro* using artificial membranes and *Xenopus* egg extracts combined with advanced microscopy and (2) investigation of how actin regulators are used by cells *in vivo* during early development in the

frog, *Xenopus laevis*. This interdisciplinary approach has two main strengths: (1) The possibility of attaining a complete molecular understanding using the *in vitro* systems and (2) study of cell biological events within the natural complement of physiological signals provided by the whole organism.

Selected publications:

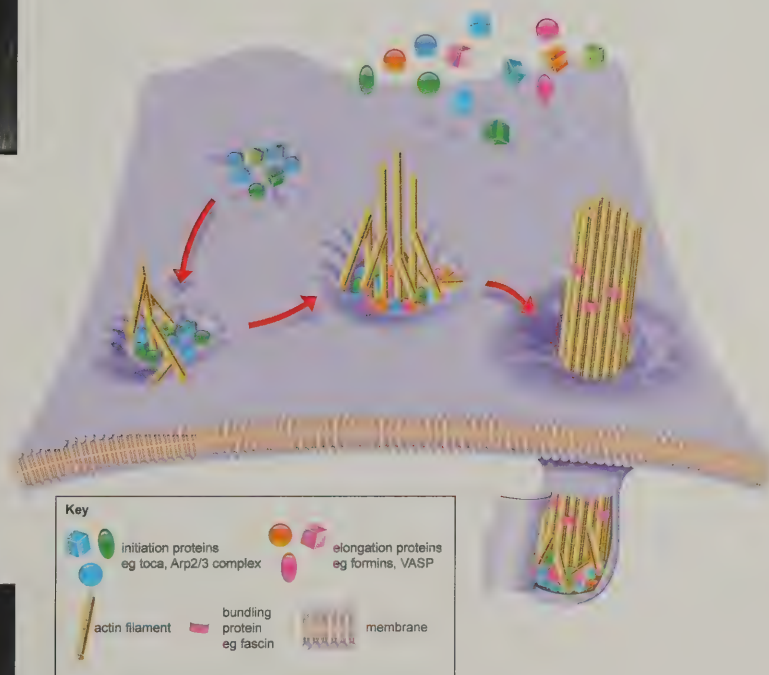
- Lee K*, Gallop JL*, Rambani K and Kirschner MW (2010) Self-assembly of filopodia-like structures on supported lipid bilayers. *Science* 329: 1341-1345
 - Gallop JL*, Jao CC*, Kent HM, Butler PJ, Evans PR, Langen R and McMahon HT (2006) Mechanism of endophilin N-BAR domain-mediated membrane curvature. *EMBO J* 25: 2898-2910
 - Gallop JL, Butler PJ and McMahon HT (2005) Endophilin and CtBP/BARS are not acyl transferases in endocytosis or Golgi fission. *Nature* 438: 675-678
 - McMahon HT and Gallop JL (2005) Membrane curvature and mechanisms of dynamic cell membrane remodelling. *Nature* 438: 590-596
- (* joint first authors)





(1) Filopodia-like structures made of fluorescently-labelled actin which grow from supported lipid bilayers (at the base of the picture).

(2) Model for filopodia formation from the study of filopodia-like structures, with an initial clustering step followed by actin polymerisation at the membrane surface then elongation of actin filaments to cause outgrowth of the filopodium.



(3) Toca localisation to lamellipodial edges, filopodia tips and endocytic vesicles in cells within a *Xenopus* gastrula explant.

John Gurdon

Nuclear reprogramming by oocytes and eggs

Co-workers: Dilly Bradford, Richard Halley-Stott, Jo-Anne Johnson, Jerome Jullien, Kei Miyamoto, Patrick Narbonne, Vincent Pasque, Marta Teperek-Tkacz, Stan Wang



The differentiated state of adult cells is remarkably stable, and ensures the normal function of our body tissues and organs. Hardly ever does a cell of one kind change into a different kind of cell. However, there are certain experimental procedures by which gene expression of a specialised adult cell can be reversed to that of an embryonic cell. This opens the way to provide therapeutically useful replacement cells of any kind from other readily available cells of another kind, such as skin.

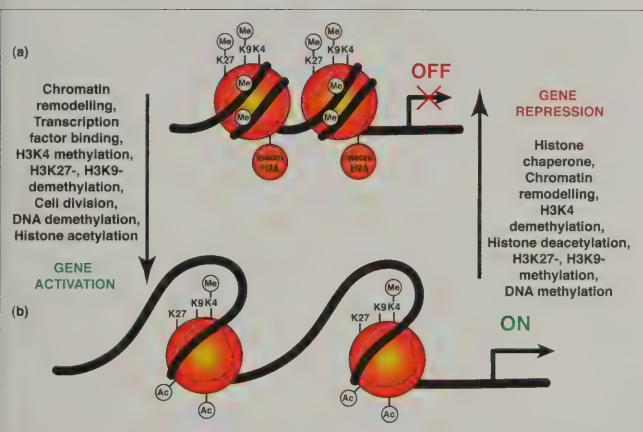
One procedure for reversing the differentiated state of a cell is by transplanting its nucleus to an egg or oocyte. Our aim is to understand how eggs or oocytes achieve this, so as to identify the reprogramming molecules involved, and thus, eventually, to improve the efficiency of this route towards cell replacement without immunosuppression.

We use the growing eggs ("oocytes") of amphibia to activate embryo-expressing genes in the transplanted nuclei of adult mammalian cells. We have recently identified polymerised actin and its cofactors as a significant component of this oocyte transcriptional apparatus for reprogramming somatic nuclei. A question of at least as much importance is how the differentiated state of a cell makes its nucleus resistant to the reprogramming activities of an oocyte. Genes that become transcriptionally repressed in normal development are of this kind. Such genes show an epigenetic memory of their quiescent state. We have identified macroH2A as one chromatin protein that helps to confer an inactive state of genes on the inactive X chromosome of female mammals. We have recently developed a procedure by which chromosomal proteins can be progressively removed from somatic cell nuclei to improve embryonic gene reactivation. This can lead to the identification of chromosomal components that resist reprogramming by oocytes. The removal of these could greatly improve the efficiency of nuclear reprogramming.

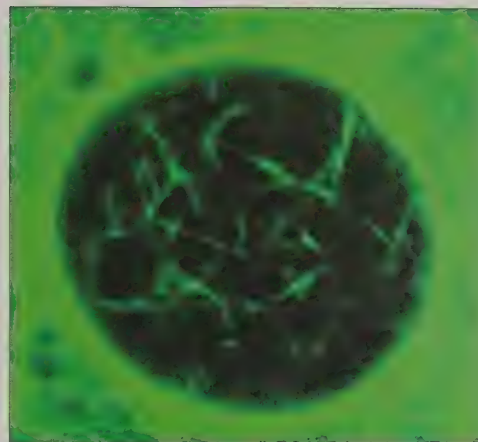
Selected publications:

- Miyamoto K, Pasque V, Jullien J and **Gurdon JB** (2011) Nuclear actin polymerization is required for transcriptional reprogramming of Oct4 by oocytes. **Genes & Development** 25(9):946-958
- Pasque V, Gillich A, Garrett N and **Gurdon JB** (2011) Histone variant macroH2A confers resistance to nuclear reprogramming. **EMBO J** 6;30(12):2373-87
- Jullien J, Halley-Stott RP, Miyamoto K, Pasque V and **Gurdon JB** (2011) Mechanisms of nuclear reprogramming by eggs and oocytes: a deterministic process? **Nature Reviews Molecular & Cell Biology**, 12, 453-459
- Narbonne P, Simpson DE and **Gurdon JB** (2011) Deficient induction response in a *Xenopus* nucleocytoplasmic hybrid. **PLoS Biology** 9(11):e101197
- Pasque V, Jullien J, Miyamoto K, Halley-Stott RP and **Gurdon JB** (2011) Genetic and epigenetic factors affecting nuclear reprogramming efficiency. **Trends in Genetics** 27(12):516-525

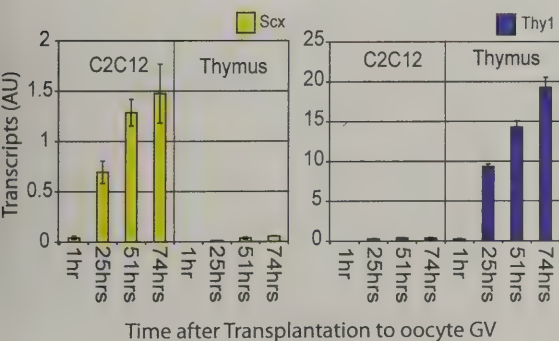




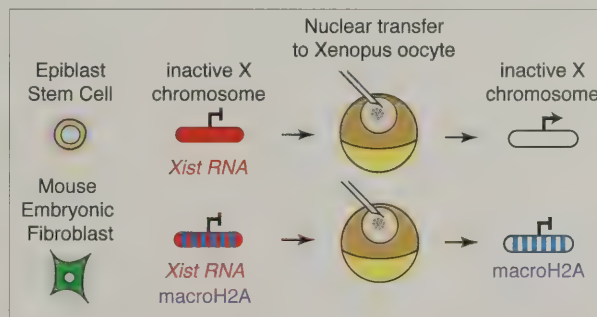
A model of changes in chromatin state during reprogramming.



Polymerised nuclear actin enhances nuclear reprogramming.



A dramatic difference exists in the ability of an oocyte to activate *Scleraxis* (*Scx*) or *Thy1* genes in different cell types.



Transcription of an inactive X chromosome of mice is inhibited in part by macroH2A.

Steve Jackson

Maintenance of genome stability

Co-workers: Linda Baskcomb, Rimma Belotserkovskaya, Melanie Blasius, Sebastien Britton, Jessica Brown, Julia Coates, Kate Dry, Josep Forment, Yaron Galanty, Ilaria Guerini, Jeanine Harrigan, Abderrahmane Kaidi, Delphine Larrieu, Carlos Le Sage, Natalia Lukashchuk, Ryotaro Nishi, Tobias Oelschlägel, Helen Reed, Christine Schmidt, Matylda Sczaniecka-Clift, Neha Thakkar, Jorrit Tjeertes, Jon Travers, Paul Wijnhoven



Our work focuses on the DNA-damage response (DDR): the set of events that optimises cell survival and genomic integrity by detecting DNA damage, signalling its presence and mediating its repair. The importance of the DDR is underscored by defects in it being associated with various pathologies, including neurodegenerative disease, immunodeficiency, developmental defects, premature ageing, infertility and cancer. Indeed, we recently identified mutations in the DDR protein CtIP that cause Seckel syndrome, a recessively inherited dwarfism disorder characterised by microcephaly, and a related disease called jawad syndrome (1).

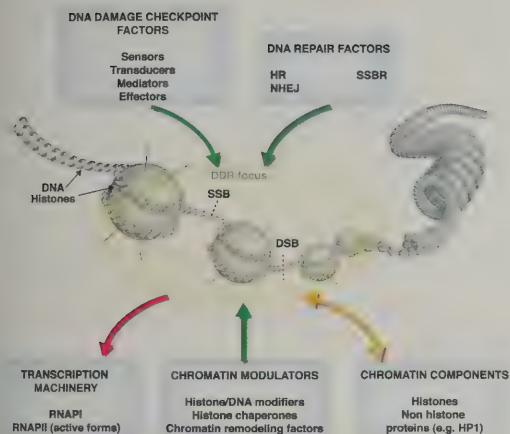
For many years, we have been studying how protein phosphorylation controls the DDR. We have now carried out phospho-proteomic screens in collaboration with Dr. Chunaram Choudhary (Copenhagen, Denmark), enabling us to identify novel substrates of the cell-cycle checkpoint kinase Chk1 (2). In addition, we identified a DNA-damage dependent phosphorylation site on the key homologous recombination protein Rad51 that controls Rad51 function (3). Furthermore, we have studied how DNA damage arises in the absence of Chk1 activity, showing that this is mediated by the endonuclease Mus81/Eme1 (4). Another recent highlight has been our data showing how DNA replication stress leads to the formation of chromosomal fragile sites in G1 phase of the next cell cycle (5). This work has thus helped our understanding of how fragile sites arise and contribute to cancer and other diseases.

In addition, our studies have led to new therapeutic opportunities. To exploit these, with the assistance of Cancer Research Technology and Cambridge University, Steve Jackson founded MISSION Therapeutics whose aim is to translate new molecular understandings of human cell biology into drugs that will markedly improve the management of life-threatening diseases, particularly cancer (<http://www.missiontherapeutics.com/>).

Selected publications:

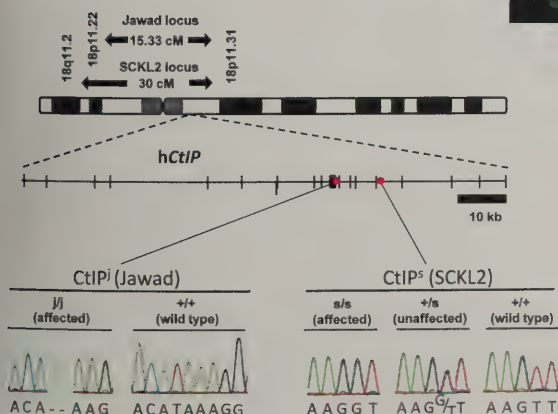
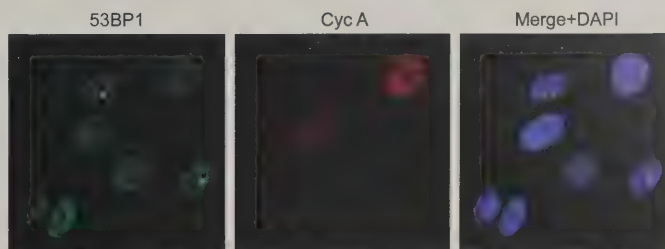
- 1) Qvist P, Huertas P, Jimeno S, Nyegaard M, Hassan MJ, **Jackson SP** and Børglum AD (2011) CtIP mutations cause Seckel and Jawad syndromes. *PLoS Genetics* 7, e1002314
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- 3) Flott S, Kwon Y, Pigli YZ, Rice PA, Sung P and **Jackson SP** (2011) Regulation of Rad51 function by phosphorylation. *EMBO Rep* 12, 833-9
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- 5) Harrigan JA, Belotserkovskaya R, Coates J, Dimitrova DS, Polo SE, Bradshaw CR, Fraser P and **Jackson SP** (2011) Replication stress induces 53BP1-containing OPT domains in G1 cells. *J Cell Biol* 193, 97-108





Protein dynamics to and from sites of DNA breaks. DNA damage checkpoint and repair factors and modulators of chromatin organization are recruited (green arrows) to DNA breaks (SSB and DSB), while transcription machineries are excluded (red arrows), and the dynamics of structural chromatin components operate in both directions (orange arrows). HR, homologous recombination; NHEJ, non-homologous end joining. Taken from Polo SE and Jackson SP (2011) Dynamics of DNA damage response proteins at DNA breaks: A focus on protein modifications. *Genes Dev* 25, 409-433

53BP1 (green) accumulates in nuclear bodies in a subset of G1 cells. Cyclin A positive cells (red) are in S/G2 phase of the cell cycle. Scale bar, 30 μ m.



Schematic genetic map of chromosome 18 with the SCKL2 and Jawad loci, defined by homozygous chromosomal segments in affected consanguineous families. The CtIP gene spans 93 kb of genomic sequence covering 19 exons (vertical bars), of which 18 are coding. Red dots indicate positions of mutations and point to sequence electropherograms of homo- and heterozygous carriers and corresponding wild-type sequence.

Tony Kouzarides

Function of chromatin modifications and their role in cancer

Co-workers Paulo Amara, Andrew Bannister, Isabella Barbieri, Gonçalo Castelo-Branco, Maria Christophorou, Alistair Cook, Mark Dawson, Sri Lestari, Nikki Parsons, Sam Robson, Helena Santos Rosa, Marc Schneider, Peter Tessarz, Emma Viré, Beata Wyspianska



Our group is interested in defining the mechanisms by which chromatin modifications function to regulate cellular processes. Our attention is focussed on a set of enzymes (acetylases, deacetylases, methylases and kinases), which regulate transcription by covalently modifying histones. We would like to understand what biological processes these enzymes control and the precise role of each modification on chromatin dynamics. In addition we are dissecting as far as possible, how modification pathways are mis-regulated in cancer cells.

Histones are very highly modified. This complexity is necessary because histones integrate many signalling pathways regulating DNA function. We are taking a number of complementary approaches to characterise the role of chromatin modifications. We are using yeast as a model system whenever possible to define new pathways and we are using human cells to characterise their function in higher organisms and probe connections to cancer.

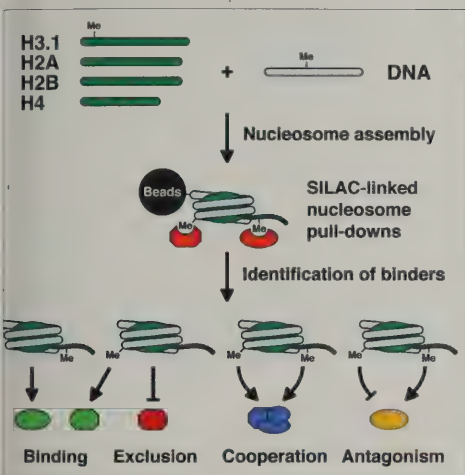
Modifications work by the recruitment of proteins. We have developed an assay for capturing proteins that recognise differentially modified nucleosomes, called SNAP (Slac Nucleosome Affinity Purification). This approach has been successfully used to identify proteins that are sensitive to nucleosomes methylated on histones and DNA thus defining categories of 'cross talk' between these two distinct classes of modification.

Recently we have shown that a set of bromodomain proteins called BET are involved in activating a set of genes regulated by MLL-fusions; the gene products responsible for MLL-leukaemia. A small molecule inhibitor of BETs, called +BET which prevents them from binding to acetylated histones is able to suppress this gene program in primary human leukaemias and halts the process of leukaemia in model systems. Together these data give hope for the development of a therapeutic agent against MLL-leukaemias.

Selected publications:

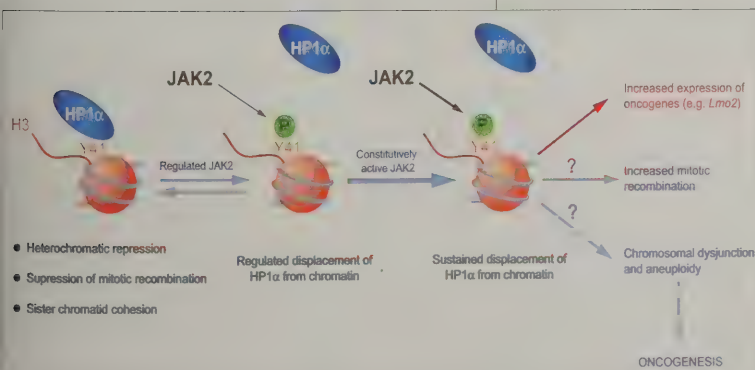
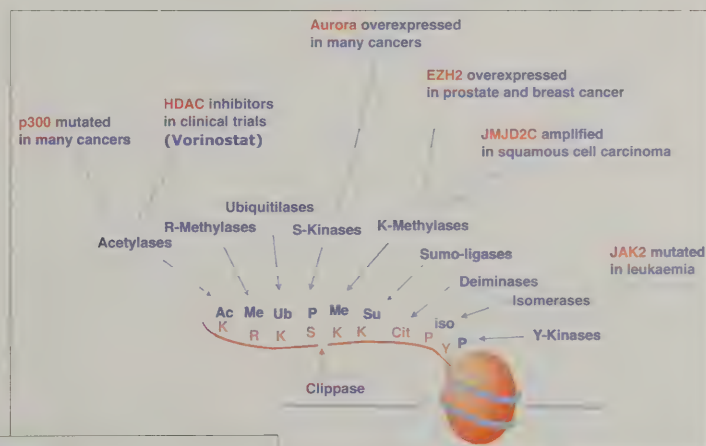
- Dawson MA, Prinija RK, Dittmann A, Giotopoulos G, Bantscheff M, Chan WI, Robson SC, Chung CW, Hopf C, Savitski MM, Huthmacher C, Gudgin E, Lugo D, Beinke S, Chapman TD, Roberts EJ, Soden PE, Auger KR, Mirguet O, Doehner K, Delwel R, Burnett AK, Jeffrey P, Drewes G, Lee K, Huntly BJ and **Kouzarides T** (2011) Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. **Nature** 478(7370), 529-533
- Bartke T, Vermeulen M, Xhemalce B, Robson SC, Mann M and **Kouzarides T** (2010). Nucleosome-interacting Proteins Regulated by DNA and Histone Methylation. **Cell** 143: 470 – 84
- Xhemalce B and **Kouzarides T** (2010) A chromodomain switch mediated by histone H3 Lys 4 acetylation regulates heterochromatin assembly. **Genes Dev** 24(7), 647-652
- Dawson MA, Bannister AJ, Göttgens B, Foster SD, Bartke T, Green AR and **Kouzarides T** (2009) JAK2 phosphorylates histone H3Y41 and excludes HP1alpha from chromatin. **Nature** 461(7265), 819-822
- Santos-Rosa H, Kirmizis A, Nelson C, Bartke T, Saksouk N, Cote J and **Kouzarides T** (2009) Histone H3 tail clipping regulates gene expression. **Nat Struct Mol Biol** 16(1), 17-22





Model for the nuclear role of JAK2 in normal cells and in leukaemias containing JAK2 mutations.

The SNAP approach identifies 'cross-talk' between modifications in nucleosomes.



Chromatin-modifying enzymes are deregulated in cancer.

Rick Livesey

Mammalian neural stem cell biology, fundamental and applied

Co-workers: Jessica Alsjö, Therese Andersson, Chibawanye Ene, Peter Kirwan, João Pereira, Nathalie Saurat, Yichen Shi, James Smith, Anthony Walsh



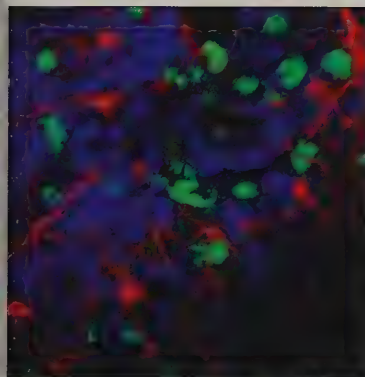
The cerebral cortex, which makes up three quarters of the human brain, is the part of the nervous system that integrates sensations, executes decisions and is responsible for cognition and perception. Given its functional importance, it is not surprising that diseases of the cerebral cortex are major causes of morbidity and mortality. Understanding the biology of cortical neural stem cells is essential for understanding human evolution, the pathogenesis of human neurodevelopmental disorders and the rational design of neural repair strategies in adults. During embryonic development, all of the neurons in the cortex are generated from a complex population of multipotent stem and progenitor cells. Much of the research in the lab centres on the cell and molecular biology of cortical stem cells. We are particularly interested in the molecular mechanisms controlling multipotency, self-renewal and neurogenesis, and how these are coordinated to generate complex lineages in a fixed temporal order. A number of ongoing projects in the group address the functional importance of transcriptional and epigenetic mechanisms in this system.

In the other major strand of research in the group, we have developed methods for directing differentiation of human pluripotent stem cells to cortical neurons, via a cortical stem cell stage. Human stem cell-derived cortical neurons form functional networks of excitatory synapses in culture. We are using this system for studies of human neural stem cell biology and to generate models of cortical diseases. Our initial focus has been on dementia, where we have used stem cells from people with Down syndrome and from patients with familial Alzheimer's disease to create cell culture models of Alzheimer's disease pathogenesis in cortical neurons. We are using those models to study Alzheimer's disease pathogenesis and the efficacy of current therapeutic strategies.

Selected publications:

- Pereira JD, Sansom SN, Smith J, Dobenecker MW, Tarakhovsky A and **Livesey FJ** (2010) Ezh2, the histone methyltransferase of PRC2, regulates the balance between self-renewal and differentiation in the cerebral cortex. **Proc Natl Acad Sci USA** 107, 15957-15962.
- Andersson T, Rahman S, Sansom SN, Alsio JM, Kaneda M, Smith J, O'Carroll D, Tarakhovsky A and **Livesey FJ** (2010) Reversible block of mouse neural stem cell differentiation in the absence of dicer and microRNAs. **PLoS ONE** 5, e13453
- Subkhankulova T, Yano K, Robinson HP and **Livesey FJ** (2010) Grouping and classifying electrophysiologically-defined classes of neocortical neurons by single cell, whole-genome expression profiling. **Front Mol Neurosci** 3, 10
- Sansom SN, Griffiths DS, Faedo A, Kleinjan DJ, Ruan Y, Smith J, van Heyningen V, Rubenstein JL and **Livesey FJ** (2009) The level of the transcription factor Pax6 is essential for controlling the balance between neural stem cell self-renewal and neurogenesis. **PLoS Genetics** 5, e1000511
- Sansom SN and **Livesey FJ** (2009) Gradients in the brain: the control of the development of form and function in the cerebral cortex. **Cold Spring Harb Perspect Biol** 1:a002519

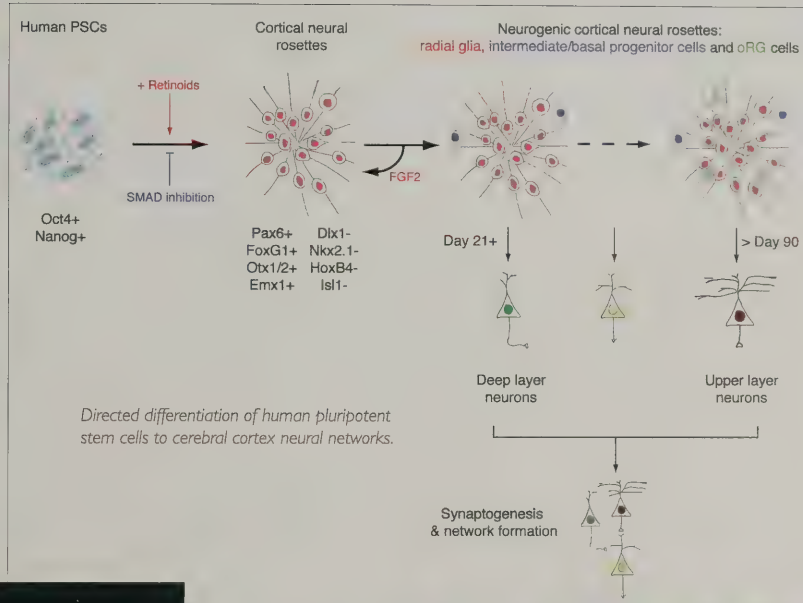




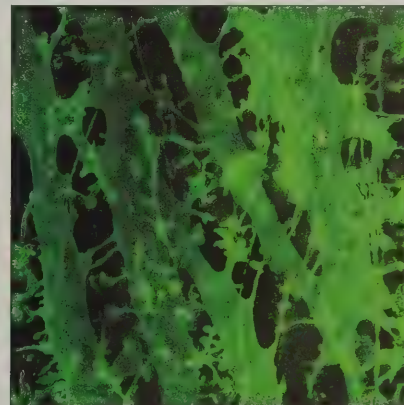
Extracellular aggregates (green) of the Alzheimer's disease pathogenic peptide Aβ42 in cultures of human cortical neurons generated from Down syndrome iPS cells.



Human cortical stem cells formed polarised neuroepithelial rosettes in culture, with centrosomes (red) located apically at the centre of the rosette.



Super-resolution microscopy image of DiO-labelled human iPS cell-derived cortical neurons



Eric Miska

Small regulatory RNA

Co-workers: Javier Armisen Garrido, Alyson Ashe, Alejandra Clark, Leonard Goldstein, Ethan Kaufman, Miranda Landgraf, Nic Lehrbach, Jeremie Le Pen, Helen Lightfoot, Sylvianne Moss, Kenneth Murfitt, Greta Pintacuda, Amie Regan, Alexandra Sapetschnig, Peter Sarkies, Eva-Maria Weick, Julie Woolford



microRNAs (miRNAs), a large class of short non-coding RNAs found in many plants and animals, often act to inhibit gene expression post-transcriptionally. Approximately 3% of all known human genes encode miRNAs. Important functions for miRNAs in animal development and physiology are emerging. A number of miRNAs have been directly implicated in human disease. We have generated loss-of-function mutations in almost all of the 112 known miRNA genes in the nematode *Caenorhabditis elegans*. This collection provides the only comprehensive resource for the genetic analysis of individual miRNAs to date. Our main goal is to understand the genetic networks underlying miRNA-dependent control of development.

We are also studying other short RNA (sRNA) species, their biology and mechanism of action. For example, we recently identified the piRNAs of *C. elegans*. piRNAs are required for germline development and maintenance in worms, flies and mammals. Neither the biogenesis nor the mechanism of action is understood for this class of small RNAs. We are using genetic screens, biochemical and molecular biology approaches to address basic questions about sRNA biology. Of particular interest is how small RNA regulatory networks interact with the genome and the environment.

In addition, we have developed tools for the analysis of miRNA expression in human disease and have discovered miRNAs that have potential as molecular markers for diagnosis and prognosis.

Selected publications:

- Lehrbach N, Armisen J, Lightfoot H, Murfitt K, Bugaut A, Balasubramanian S, **Miska EA** (2009) LIN-28 and the poly(U) polymerase PUP-2 regulate let-7 microRNA processing in *Caenorhabditis elegans*. **Nature Struct Mol Biol** 16, 1016-1022

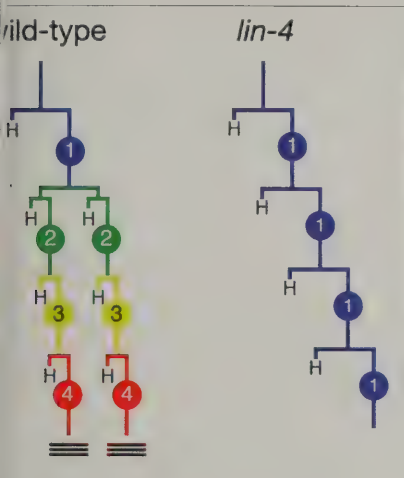
- Armisen J, Gilchrist MJ, Wilczynska A, Standart N and **Miska EA** (2009) Abundant and dynamically expressed miRNAs, endo-siRNAs and piRNAs in the African clawed frog *Xenopus tropicalis*. **Genome Research** 19, 1766-1755

- Das PP, Bagijn MP, Goldstein LD, Woolford JR, Lehrbach NJ, Sapetschnig A, Buhecha HR, Gilchrist MJ, Howe KJ, Stark R, Berezikov E, Ketting RF, Tavaré S, **Miska EA** (2008) Piwi and piRNAs act upstream of an endogenous siRNA pathway to suppress Tc3 transposon mobility in the *Caenorhabditis elegans* germline. **Mol Cell** 31, 79-90

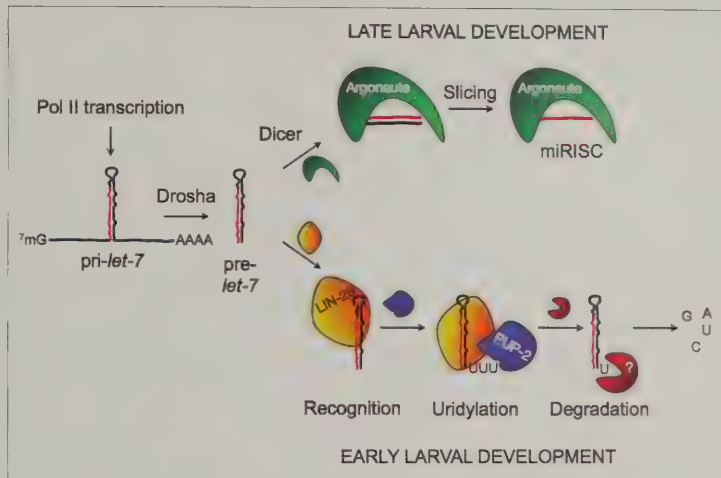
- **Miska EA**, Alvarez-Saavedra E, Abbott AL, Lau NC, Hellman AB, Bartel DP, Ambros VR, Horvitz HR (2007) Most *Caenorhabditis elegans* microRNAs are individually not essential for development or viability. **PLoS Genet** 3, e215

- Clark AM, Goldstein LD, Tevlin M, Tavaré S, Shaham S, **Miska EA** (2010) The microRNA miR-124 controls gene expression in the sensory nervous system of *Caenorhabditis elegans*. **Nucleic Acids Res** 38(11):3780-93, Epub 2010 Feb 21

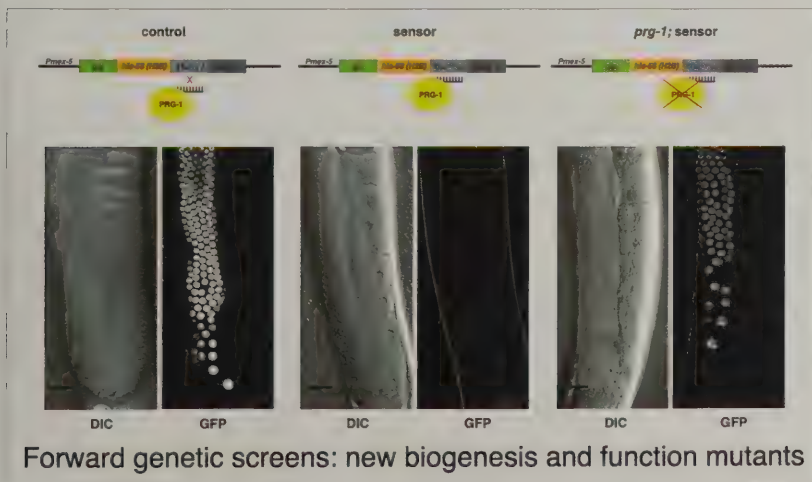




first miRNA to be identified was the product of *C. elegans* gene *lin-4*. Loss of function of *lin-4* leads to the failure of a stem cell lineage to differentiate.



We have discovered that *let-7*, *LIN-28* and the poly(U) polymerase form an ultraconserved switch that regulates stem cell decisions in *C. elegans*.



An in-vivo assay for piRNA function in the germline. piRNAs and Piwi proteins protect the germline. We are using molecular genetics, cell biology and high-throughput sequencing to discover miRNA biogenesis and mechanisms.

Eugenia Piddini

Competitive cell interactions in normal physiology and cancer

Co-workers: Laura Blackie, Alexis Braun, Maja Goschorska, Golnar Kolahgar, Carolina Mendoza-Topaz, Kathy Oswald, Enzo Poirier, Benjamin Smith, Silvia Vivarelli, Laura Wagstaff



Cell interactions are at the basis of all multi-cellular life. They allow cells to coordinate decisions such as whether to proliferate, differentiate or die and are therefore essential to generate and maintain healthy tissues and organs. Our lab studies the mechanisms and the physiological role of competitive cell interactions. These interactions were first discovered in *Drosophila* when it was found that, within tissues, cells compete for survival and less fit cells are induced to die.

We have recently found that, in *Drosophila*, cells with different signalling levels of the growth factor Wingless (the *Drosophila* homolog of the mammalian Wnt family oncogene Wnt-1) engage in cell competition and, in particular, that cells with abnormally high signalling levels induce the death of neighbouring wild-type cells. Since Wnt signalling is overactivated in a variety of cancers, Wnt-induced cell competition could allow cancer cells to kill surrounding normal cells during early tissue colonisation.

Based on these observations, our current work is expanding in two main directions. First, we want to understand at the molecular level how this newly-discovered type of competition is brought about. To this end, we are using the power of *Drosophila* genetics to investigate how cells sense differential Wingless signalling levels among them, and what molecules they exchange that lead to the selective elimination of low Wingless signalling cells. Secondly, we want to investigate the relevance of this phenomenon in Wnt-induced cancers. For that purpose, we are working towards reconstituting Wnt-induced cell competition between normal cells and Wnt-induced tumour cells in culture. This will allow us to translate our findings from *Drosophila* to mammals and to identify novel mediators of cell competition of potential therapeutic relevance.

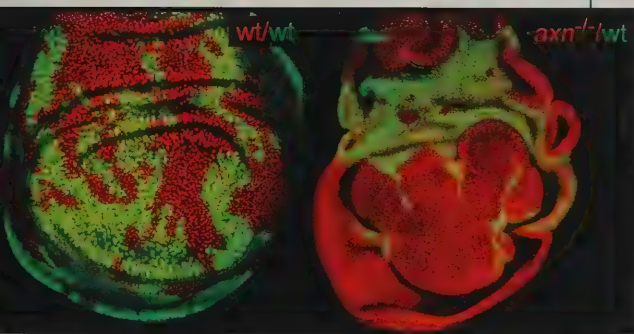
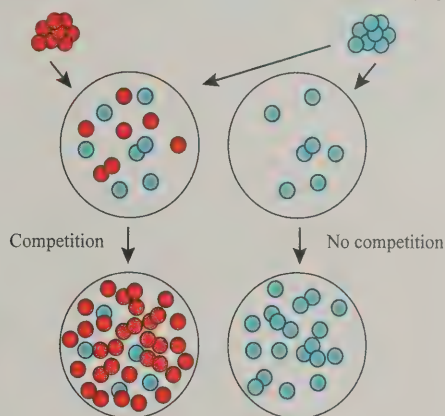
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- Piddini E and Vincent JP (2009) Interpretation of the Wingless gradient requires signalling-induced self-inhibition. *Cell* Jan 136, 296-307
- Piddini E*, Marshall F*, Dubois L, Hirst E, Vincent JP (2005) Arrow (LRP6) and Frizzled2 cooperate to degrade Wingless in *Drosophila* imaginal discs. *Development* Dec;132(24):5479-89. * equal contribution
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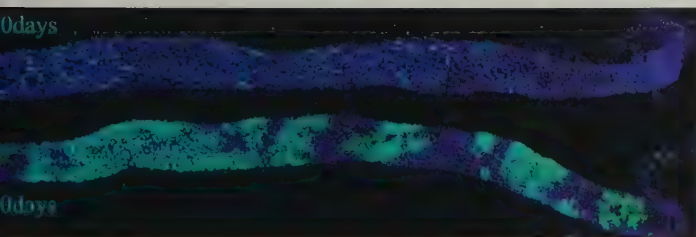
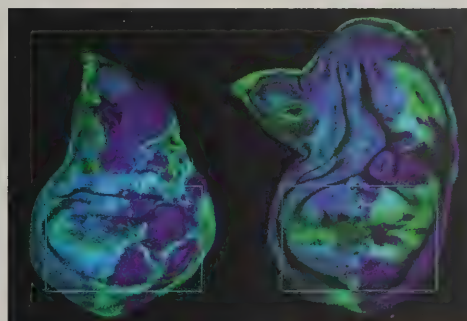
We are working towards reconstituting cell competition among tumour cells and normal cells *in vitro*. We do so by mixing them in culture and analysing how this affects the proliferation and survival of normal cells.

Winners: cancer cells **Losers: non-cancer cells**



a control disc, where both GFP-positive and GFP-negative cells are wild-type, they colonise the tissue equally (left panel). However when GFP-negative cells have high-Wnt signalling they outcompete wild-type GFP-positive cells (right panel).

Left panel: High Wnt signaling cells (GFP-negative) generated in the Posterior compartment of a wing pouch (boxed area) colonise the tissue at the expense of wild-type cells. Right panel: By contrast, in a notum mutant background outcompetition by high Wnt signaling cells is inhibited.



Like in the mammalian colon, overactivation of Wnt signaling leads to adenomas in the *Drosophila* gut. High-Wnt cells (green) overproliferate and form extensive adenomas 20 days after induction. The top gut was fixed 10 days after high-Wnt cells generation. The bottom gut was fixed 20 days after high-Wnt cells generation.

Jonathon Pines

How do cells control mitosis?

Co-workers: Philippe Collin, Barbara Di Fiore, Anja Hagting, Daisuke Izawa, Mark Jackman, Agata Lichawska, Jörg Mansfeld, Paola Marco, Takahiro Matsusaka, Oxana Nashchekina, Bernhard Strauss, Samuel Wieser



How do cells regulate entry to mitosis? And, once in mitosis, how do cells coordinate chromosome segregation with cell division (cytokinesis) to ensure that the two daughter cells receive an equal and identical copy of the genome? The answer lies in the interplay between protein kinases, protein phosphatases, and APC/C-mediated proteolysis, and this is the focus of our research. Because mitosis is a highly dynamic process we study living cells by time-lapse fluorescence microscopy but to complement this with biochemical analyses we are using somatic cell recombination to knock-out and mutate specific mitotic regulators. This has given us remarkably accurate and precise *in vivo* kinetics for protein degradation.

To understand how cells initiate mitosis we are analysing the behaviour of the key mitotic kinases, the Cyclin A- and B-dependent kinases, and their regulation by phosphorylation and dephosphorylation. We recently developed a FRET biosensor to assay Cyclin B1-Cdk1 activity *in vivo* and are using this to define the pathways that regulate the timing of mitosis. To identify the proteins responsible for regulating the Cyclin-Cdks, and provide insights into Cyclin-Cdk substrates, we have analysed protein complexes through the cell cycle by SILAC mass spectrometry and are following up some of the exciting results from this screen.

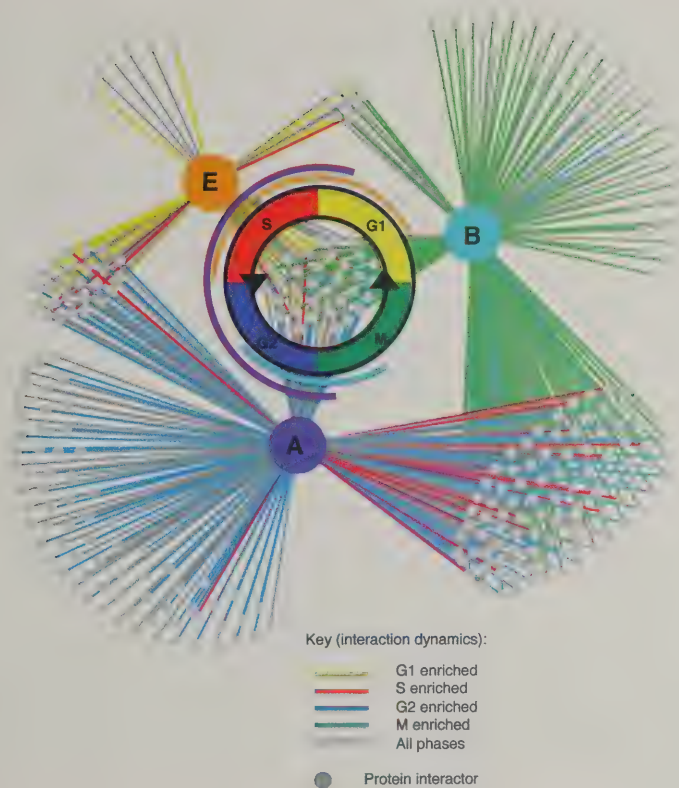
To understand how proteolysis regulates progress through mitosis we complement the analysis of APC/C-dependent degradation in living cells with biochemical analyses of protein complexes and ubiquitination activity. These studies are revealing how the APC/C is activated and how it is able to select a particular protein for destruction at a specific time. Our research is also providing insights into how APC/C activity is regulated by the spindle assembly checkpoint that is essential to the control of chromosome segregation and cytokinesis. In particular, we are beginning to elucidate the key events in the checkpoint pathway and their antagonism by the APC/C itself.

Selected publications:

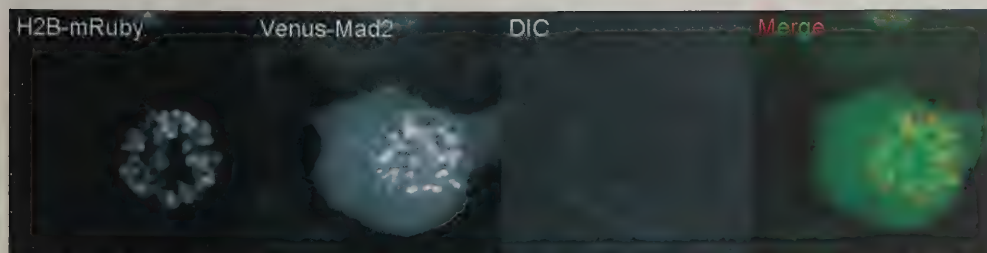
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- Gavet O and Pines J (2010) Progressive activation of Cyclin B1-Cdk1 coordinates entry to mitosis. *Dev Cell* 18, 533-543.
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Mass spectroscopy analysis reveals the dynamic interactions of the different cyclins through the cell cycle.
Credit: Felicia Walton-Pagliuca & Mark Collins (Sanger Institute)



Montage of a prometaphase cell in which the Venus fluorescent protein has been knocked into the Mad2 locus. Mad2 binds to unattached kinetochores. The chromosomes are labelled with ectopically expressed Histone H2B-mRuby. (Philippe Collin, 2010)



Emma Rawlins

Stem and progenitor cells in the mammalian lung

Co-workers: Gayan Balasooriya, Christoph Budjan, Simon Gerber, Usua Laresgoiti, Rachel Seear



Our lungs have a complex three-dimensional structure which facilitates respiration and host defence. Building this structure requires that lung embryonic progenitor cells produce the correct types and numbers of cells in the correct sequence. How is this controlled? And how is the final structure maintained in the adult? Our lab investigates the cellular and molecular mechanisms which control stem and progenitor cell fate decisions in the developing and adult lungs. Key unanswered questions include what mechanisms control the decision of lung progenitors to self-renew or to differentiate? Which pathways are required for cell lineage specification in the lung? Our approach is to use the power of mouse genetics to understand the control of lung progenitor cell behaviour at the single cell level. This allows individual cells to be analysed quantitatively *in vivo*, or by live-imaging in organ culture systems.

We have previously shown that in the embryonic lung there is a population of Id2+ multipotent epithelial progenitor cells located at the distal tips of the budding epithelium. The developmental potential, or competence, of these cells changes during embryogenesis. At the same time the cells undergo a change in gene expression pattern. We are currently exploring the cellular and molecular basis of this change in competence.

The identity of the epithelial stem and progenitor cells in the postnatal lung remains controversial. Our previous work has shown that each anatomical region (trachea, bronchioles, alveoli) has its own progenitor cell population and that the behaviour of these progenitors can change in response to local conditions. Our current postnatal work focuses on:

- Better characterising the adult lung progenitor cells. This includes testing whether progenitor cell behaviour is widespread or there are stem cells.
- Understanding the genetic regulation of the progenitors under several different physiologically-relevant conditions. In particular, we are focusing on genes that are

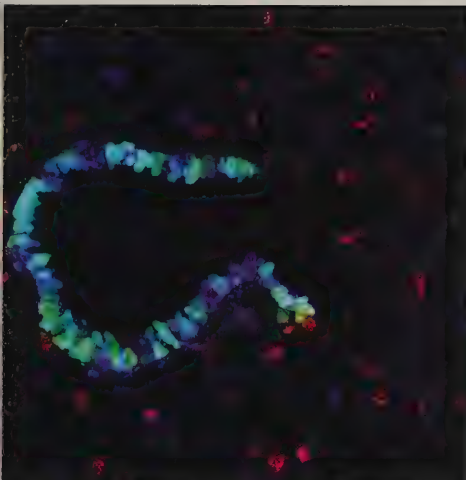
hypothesised to control the decision to self-renew or differentiate.

Our long-term vision is to combine the developmental and homeostatic aspects of our work to develop new approaches to ameliorate human pulmonary disease. In particular, we are working towards being able specifically to direct endogenous lung stem cells to generate any lung epithelial cell type.

Selected publications:

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- **Rawlins EL**, Clark CP, Xue Y and Hogan BLM (2009) The Id2 distal tip lung epithelium contains individual multipotent embryonic progenitor cells. **Development** 136 3741-3745
- **Rawlins EL** (2011) The building blocks of mammalian lung development. **Developmental Dynamics** 240 463-76
- Onaitis M, D'Amico TA, Clark C, Guinney J, Harpole DH and **Rawlins EL** (2011) A 10-gene progenitor cell signature predicts prognosis in lung adenocarcinoma. **Annals of Thoracic Surgery** 91 1046-50





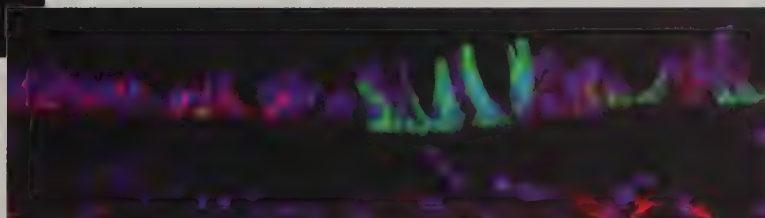
Adult mouse lung section showing lineage-labelled secretory cells (green) in the conducting airways.



Mouse embryonic lung undergoing branching morphogenesis, stained to show the epithelium (E-cadherin).



Mouse embryonic lung growing in culture. Blue (X-gal staining) shows grafted stem cells which have been incorporated into the lung structure.



A clone of mutant tracheal epithelial cells labelled with GFP (green).

Ben Simons

Patterns of stem cell fate in adult and developing tissues

Co-workers: John Biggins (Harvard), Allon Klein (Harvard), Gen Zhang



Theories of tissue maintenance place stem cells at the apex of proliferative hierarchies, possessing the lifetime property of self-renewal. In homeostasis the number of stem cells remains fixed imposing an absolute requirement for fate asymmetry in the daughters of dividing stem cells, such that only half are retained as stem cells. Fate asymmetry can be achieved either by being the invariant result of every division or by being orchestrated from the whole population, where cell fate following stem cell division is specified only up to some probability. These alternative models suggest different mechanisms of fate regulation, yet their identification in most tissues remains elusive.

In recent years, much emphasis has been placed on resolving the extrinsic factors controlling stem cell fate and the spatial organisation associated with the stem cell niche. Guided by the paradigm of invariant asymmetry, many studies have sought to identify factors that provide proliferative control, and ensure stem cell longevity. However, by addressing long-term lineage tracing studies involving several adult tissue types, from interfollicular epidermis and intestine to germ line, we have found that stem cell loss, leading to population asymmetric renewal, is central to homeostasis.

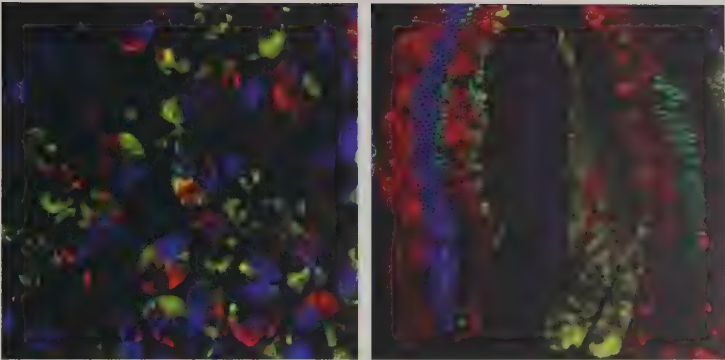
By drawing upon concepts from the statistical physics and mathematical literature, we have shown that tissue homeostasis permits just three classes of stem cell behaviour, discriminated by universal patterns of long-term clonal evolution. As well as achieving a functional classification of tissue stem cell types, this identification provides a general framework that we are using to interpret lineage tracing and mosaic-chimera studies, and to explore mechanisms of dysregulation. Current collaborators include Hans Clevers, Phil Jones, Alfonso Martinez-Arias, Michael Shen, Colin Watts, Doug Winton, and Shosei Yoshida.

In a separate but related programme of research we are also using these general concepts and lineage tracing methodologies to elucidate patterns of progenitor cell fate in the late stage development of retina and spinal cord. Current collaborators include James Briscoe, Bill Harris, and Michel Cayouette.

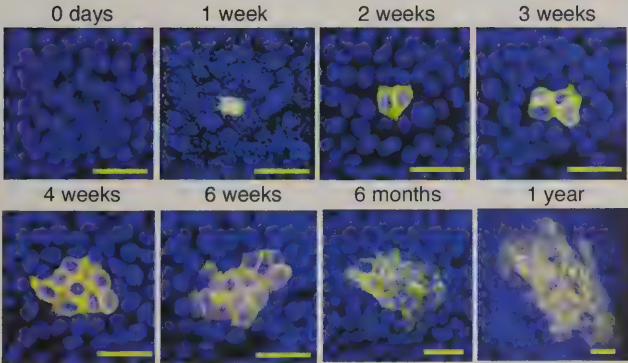
Selected publications:

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- Lopez-Garcia C, Klein AM, **Simons BD**, and Winton DJ (2010) Intestinal stem cell replacement follows a pattern of neutral drift. *Science* 330, 822-825
- Klein AM, Nakagawa T, Ichikawa R, Yoshida S, and **Simons BD** (2010) Mouse germ line stem cells undergo rapid and stochastic turnover. *Cell Stem Cell* 7, 214-224
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Studies of clonal fate using a multi-colour inducible genetic labelling system provide a vivid demonstration of neutral drift dynamics and the progression towards monoclonality in crypt. The left-hand image shows a section through the base of the crypt showing the clonal progeny of the stem/paneth cell compartment at 7 days post-induction. The right-hand image shows the migration streams of differentiated cells moving up (fully-clonal crypts) and onto villi.

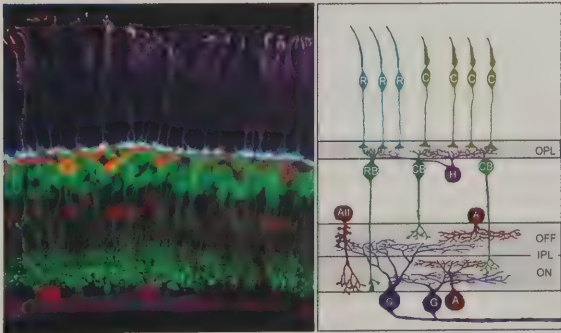


b



The confocal sections through the basal layer of interfollicular epidermis show the clonal progression of a set of progenitor cells induced at a sequence of timepoints. The data show the continual expansion of clones from an ever-diminishing clone population. A detailed analysis of the lineage-tracing data show that tissue is maintained by a single progenitor cell population following a pattern of balanced stochastic fate in which stem cell loss is compensated by self-renewal.

Lineage-tracing studies show that mechanisms of stochastic stem cell fate play a central role in the homeostasis of adult tissues. However, it remains unclear whether such patterns of fate play a role in the development of tissue. Currently, we are working with experimentalists to resolve the pattern of progenitor cell fate in retina, where retinal precursors must coordinate to give rise to multiple differentiated cell types.



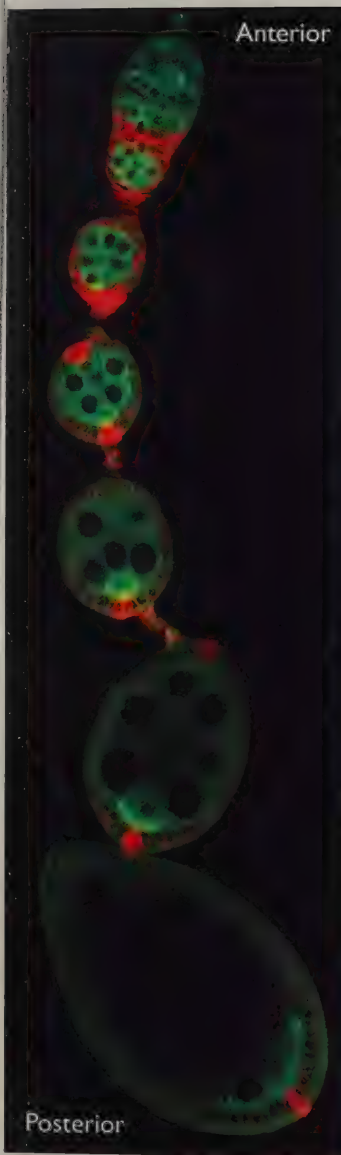
Cell polarity, the cytoskeleton and mRNA localisation



In parallel, we are examining how the *Drosophila* oocyte is polarised, since the localisation of *bicoid* and *oskar* mRNAs to opposite ends of this very large cell defines the anterior-posterior axis of the embryo. We are using proteomic and biochemical approaches to elucidate how conserved polarity proteins regulate the organisation of the microtubule cytoskeleton in the oocyte, and we are investigating the mechanisms of mRNA transport by making time-lapse films of moving mRNA particles in wildtype and mutant oocytes. In addition, we are performing genetic screens for mutants that affect the localisations of *bicoid* and *oskar* mRNAs, and are analysing the novel polarity and mRNA localisation factors that these identify.

- Doerflinger H, Vogt N, Torres IL, Mirouse V, Koch I, Nusslein-Volhard C and **St Johnston D** (2010) Bazooka is required for polarisation of the *Drosophila* anterior-posterior axis. **Development** 137, 1765-73
- Morais-de-Sa E, Mirouse V and **St Johnston D** (2010) aPKC phosphorylation of Bazooka defines the apical/lateral border in *Drosophila* epithelial cells. **Cell** 141, 509-23
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- Mirouse V, Christoforou CP, Fritsch C, **St Johnston D** and Ray R (2009) Dystroglycan and Perlecan provide a basal cue that is required for epithelial polarity during energetic stress. **Dev Cell** 16, 83-92
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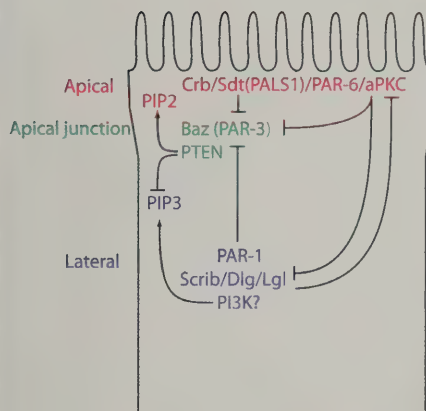




A *Drosophila* ovariole containing a series of germ line cysts that progress through oogenesis as they move posteriorly. The cysts are born at the anterior of the ovariole, and become surrounded by somatic follicle cells (red, FasIII). Each cyst contains 16 germ cells, one of which becomes the oocyte and accumulates higher levels of BicD protein (green).



Removal of the AMP-dependent protein kinase from clones of follicle cells (marked by the absence of GFP, green) causes the cells to lose their polarity and overproliferate, resulting in small tumours.



A model showing the polarity factors that mark different cortical domains in epithelial cells and the inhibitory interactions between them.



A stage 10 egg chamber expressing a marker for the microtubule minus ends fused to Cherry fluorescent protein (red), counterstained for DNA (blue). The minus ends of the microtubules are anchored to the anterior cortex of the oocyte and direct the localisation of bicoid mRNA.

Azim Surani

Principles and programming of the mammalian germ line

Co-workers: Delphine Cougot, Lynn Froggett, Astrid Gillich, Nils Grabole, Ufuk Gunesdogan, Jamie Hackett, Naoko Irie, Shinseog Kim, Caroline Lee, Harry Leitch, Erna Magnusdottir, Kazuhiro Murakami, Roopsha Sengupta, Qin Si, Julia Tischler, Katarzyna Wilczynska, Jan Zyllicz



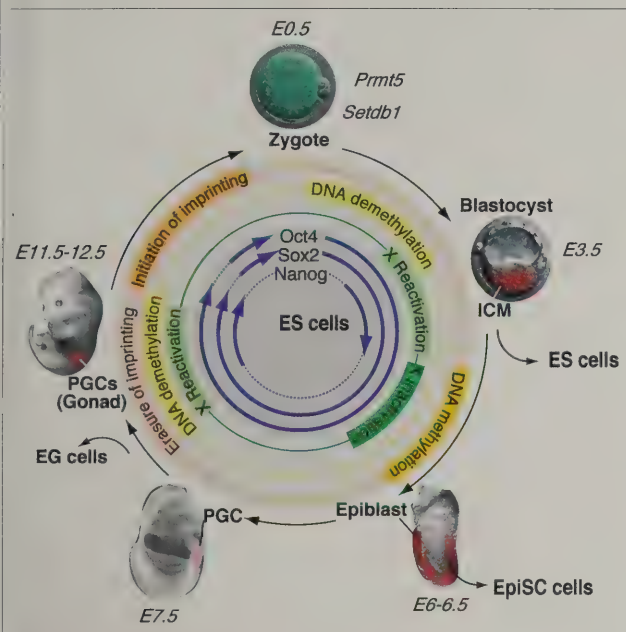
The primary objective of our research is to elucidate the mechanism of primordial germ cell (PGC) specification, and to investigate the mechanism of extensive epigenetic reprogramming in early germ cells, and by the maternally inherited factors in oocytes. Building on our previous work on germ cell determinants, we aim to resolve comprehensively the molecular foundations of specification of the mammalian germ cell lineage. Specification of PGCs is accompanied by the repression of the somatic programme, and epigenetic modifications that erase the epigenetic memory of their trajectory towards the somatic fate, while restoring an underlying pluripotency. Whereas a repressive complex maintains unipotency of germ cells, dedifferentiation of unipotent PGCs to pluripotent stem cells *in vitro* is accompanied by the reversal of the PGC specification process. Early germ cells also exhibit unprecedented epigenetic reprogramming, genome-wide DNA demethylation and chromatin remodelling, which are essential towards the establishment of totipotency. These events together with the maternal inheritances of genetic and epigenetic regulators in oocyte are critical towards the establishment of the pluripotent state. We are gathering insight into the mechanisms involved, and continuing to identify the key factors that are crucial at these times. We are interested in exploiting the knowledge gained from studies on germ cells by creating *in vitro* models for induced epigenetic reprogramming, and using these models towards attempts at rejuvenation of somatic cells.

Selected publications:

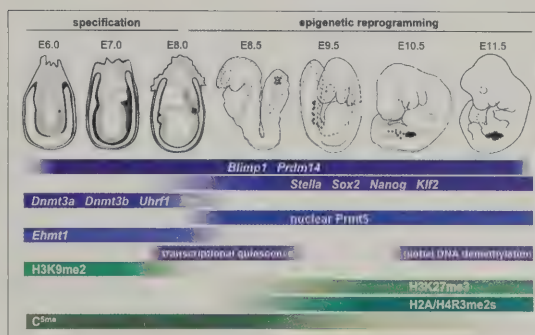
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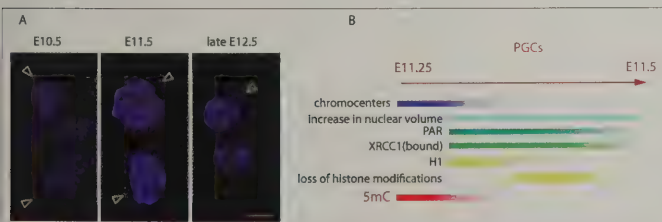
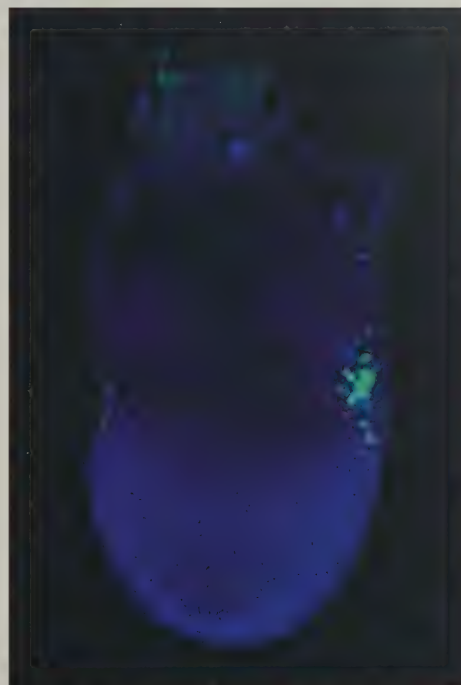


Mouse germ line cycle with the origin of primordial germ cells and pluripotent stem cells. PGC specification is accompanied by unprecedented genome-wide epigenetic program, including DNA demethylation and chromatin modifications. Maternal inheritance of epigenetic modifiers in the zygote is critical for the establishment of the pluripotent state



Overview of epigenetic reprogramming in early germ cells following PGC specification.

Figure 2. Mouse E7.5 embryo with founder PGCs detected by Stella-GFP reporter (Surani, 2010)



A) Changes in nuclear morphology and loss of chromocenters in gonadal PGCs.
B) Genome-wide DNA demethylation is accompanied by base excision repair.

Philip Zegerman

The regulation of DNA replication initiation in eukaryotes

Co-workers: Davide Mantiero, Vincent Gaggioli, Oleg Kovalevskiy, Christine Hänni, Barbara Schöpf



To successfully pass on its genetic information, every cell must make a perfect duplicate of the genome in every cell cycle. Failure to copy every chromosome faithfully leads to genomic instability, which is the cause of cancer. As a result, replication initiation is strictly regulated, both within the normal cell cycle and after DNA damage. We are interested in how this regulation of DNA replication is achieved in eukaryotes during the cell cycle and when replication forks stall.

Unlike prokaryotes, eukaryotes replicate their genomes from multiple origins. This has the advantage of facilitating the evolution of much larger and more complex genomes, but it does create a problem: If there are multiple origins in the genome, how is origin firing coordinated to make sure that no origin fires more than once?

The assembly of the eukaryotic replication apparatus at origins is tightly regulated in two critical steps. The first step, pre-replicative complex (pre-RC) formation, involves the loading of the replicative helicase Mcm2-7 in an inactive form at origins. This complex can only form in G1 phase of the cell cycle when the APC/C is active and CDK activity is low. This is because CDKs and other APC/C targets such as Geminin are potent inhibitors of pre-RC formation. Once cells enter S-phase, the APC/C is inactivated, CDK activity (and also Geminin) rises and any further pre-RC formation is blocked.

In addition to its role as an inhibitor of pre-RC formation, CDK, together with a second kinase - DDK (Cdc7/Dbf4), are essential for the second step in replication initiation, which involves the activation of the Mcm2-7 helicase and the recruitment of DNA polymerases to origins. We have previously shown that CDK phosphorylates the two essential initiation factors Sld2 and Sld3, which in turn allows binding to another essential initiation factor called Dpb11. How CDK phosphorylation of these targets facilitates replication initiation is not known, but the transient association of these factors at origins has been termed the pre-initiation complex (pre-IC). Since CDK activity both inhibits pre-RC formation and is essential to initiate replication, this produces a switch that only allows replication initiation in S-phase.

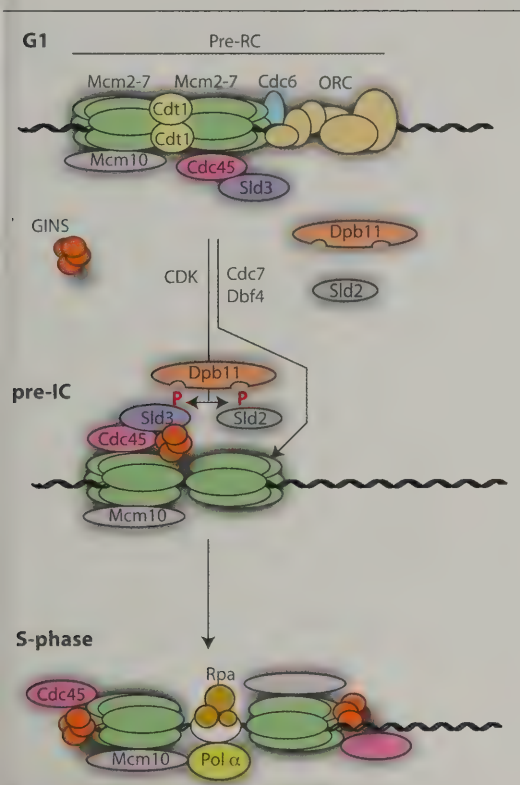
Our research is focused on the pre-initiation complex step in the replication reaction. This step is the key CDK

regulatory step, but the function of this intermediate is not known. Furthermore, the pre-IC also integrates information from other kinases, such as the DNA damage checkpoint and may be responsible for regulating how efficiently and when an origin fires during S-phase. Much of our understanding of the pre-IC in eukaryotes comes from studies in budding yeast, but how replication initiation is regulated in other eukaryotes is largely unknown. Our aim is to take advantage of the expertise in the wide variety of organisms within the institute and extend these budding yeast studies to the nematode *C. elegans* and to mammalian cells.

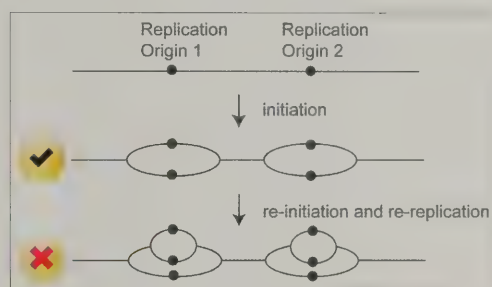
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- Walton-Pagliuca F, Collins M, Zegerman P, Choudhary J and Pines J (2011) Quantitative proteomics reveals the basis for the biochemical specificity of the cell cycle machinery. **Mol Cell** 43, 406-417
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- Zegerman P and Diffley JF (2007) Phosphorylation of Sld2 and Sld3 by cyclin-dependent kinases promotes DNA replication in budding yeast. **Nature** 445, 281-285

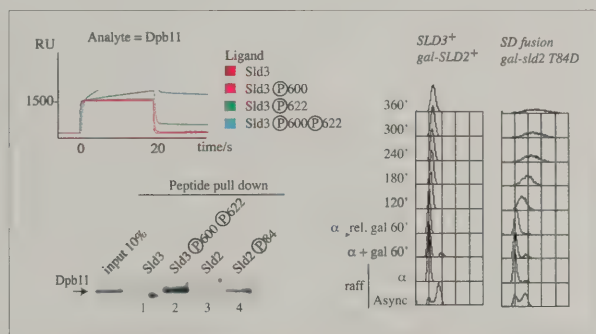




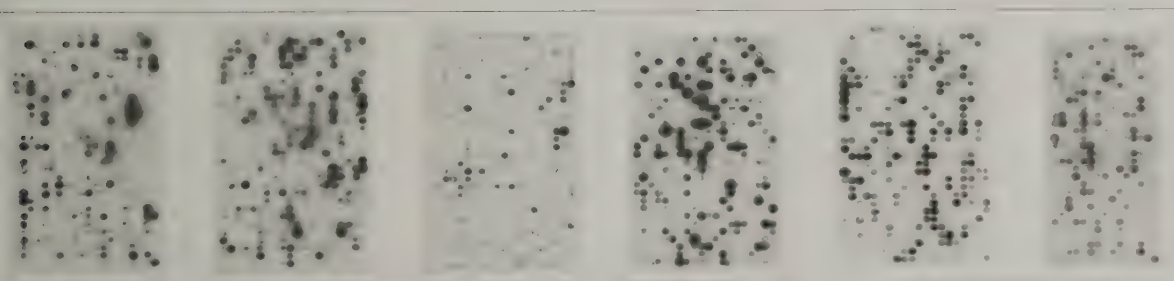
The sequence of eukaryotic replication initiation



Replication initiation must be strictly controlled to occur once, and only once, in every cell cycle.



Interactions between Dpb11 and phospho-Sld2/Sld3 in vitro (left panel) are confirmed to be essential for replication initiation in vivo (right panel).



Phospho-peptide array analysis of replication initiation factors.

Magdalena Zernicka-Goetz

Regulation and dynamics of cell fate transitions and morphogenesis during development of the early mouse embryo

Co-workers: Anna Ajduk, Stoyana Alexandrova, Paula Almeida Coelho, Florencia Barrios, Helen Bolton, John Crang, Sarah Graham, Agnieszka Jedrusik, Manuela Monti, Maryna Panamarova, Maria Skamagki, Clara Slade, Bernhard Strauss, Krzysztof Wicher, Chuen Yan Leung



Setting aside the pluripotent cells that give rise to the future body from the extra-embryonic tissues is key to early mammalian development. It requires that some blastomeres divide asymmetrically to direct cells to the inside of the embryo, where they retain pluripotency. Is this regulated or does it occur at random and then what makes inside and outside cells different from each other? To address these questions, we have traced the origins and followed the division orientations and fates of every single cell in three-dimensional space throughout the first four days of development of mouse embryos. This revealed a spatial and temporal pattern of symmetric versus asymmetric cell divisions that depends on a cell's history and defines the orientation of the embryonic-abembryonic axis of the embryo. Our findings suggest that the first cell fate decision of the mouse embryo is a result of the generation of heterogeneity among blastomeres and this affects whether blastomeres undertake symmetric or asymmetric divisions. Our recent studies show that second fate decision that leads to the formation of the second extra-embryonic tissue is bound up with the later asymmetric divisions. Currently we are addressing:

- The role of epigenetic modifications at very early stages, specifically histone H3 arginine 26 methylation that we found affects the extent of cell pluripotency.
- The cellular mechanisms regulating asymmetric divisions.
- The contributions of cell polarity and cell position in determining specific patterns of gene expression in both fate decisions.
- How the first signalling centres arise in the two extra-embryonic tissues and function immediately after implantation.

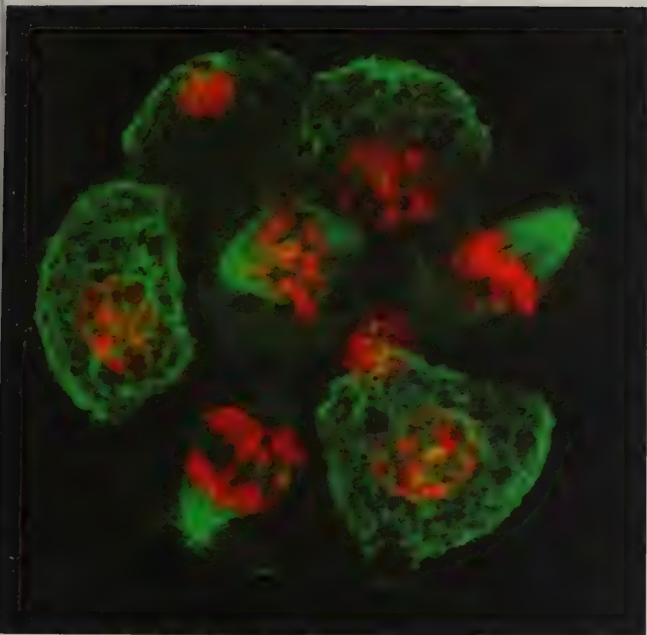
To address these questions we combine methods of classical experimental embryology with modern 4D time-

lapse microscopy and molecular cell biology techniques that we have previously developed or optimised in the lab.

Selected publications:

- Ajduk A, Ilizue T, Windsor S, Yu Y, Seres KB, Bompfrey RJ, Tom BD, Swann K, Thomas A, Graham C and **Zernicka-Goetz M** (2011) Rhythmic actomyosin-driven contractions induced by sperm entry predict mammalian embryo viability **Nature Communications** 2, Article number: 417 doi:10.1038/ncomms1424
- Morris SA, Teo RT, Li H, Robson P, Glover DM, and **Zernicka-Goetz M** (2010) Origin and formation of the first two distinct cell types of the inner cell mass in the mouse embryo. **Proc Natl Acad Sci USA** 6;107(14):6364-9
- **Zernicka-Goetz M**, Morris S and Bruce A (2009) Making a firm decision: layers of regulation in early mouse embryo. **Nature Rev Genet** 10, 467-77
- Jedrusik A, Parfitt DE, Guo G, Skamagki M, Grabarek JB, Johnson MH, Robson P and **Zernicka-Goetz M** (2008) Role of Cdx2 and cell polarity in cell allocation and specification of trophectoderm and inner cell mass in the mouse embryo. **Genes Dev** 22, 2692-706

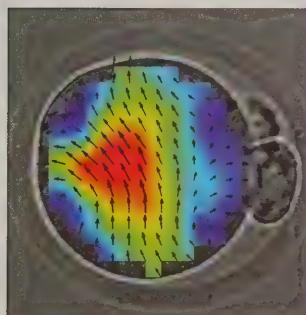




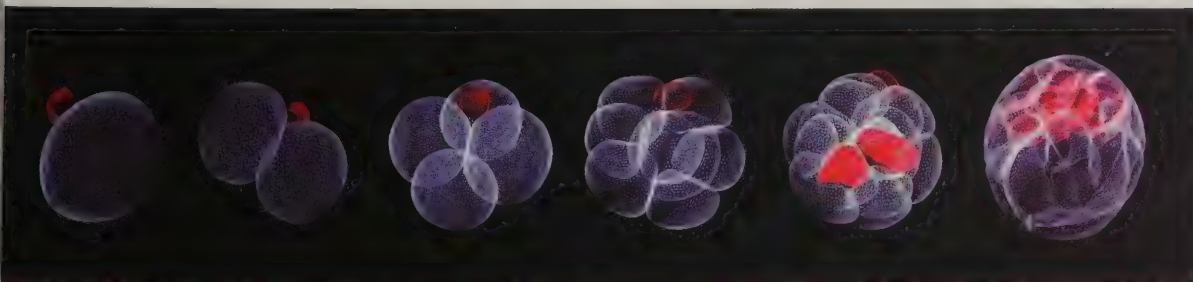
3D projection of a dividing 8 cell stage embryo (DNA, in red and α -tubulin, in green).



3D reconstruction of the mouse embryo (16-cell stage).



The cytoplasmic flows in a fertilised mouse egg



3D reconstructions of preimplantation mouse development.

CATEGORIES OF APPOINTMENT

SENIOR GROUP LEADER

Professor, Reader or Director of Research

GROUP LEADER

5-year grant-funded appointment (maximum 10 years)

CAREER DEVELOPMENT FELLOW

4-year grant-funded appointment

INDEPENDENT SENIOR RESEARCH ASSOCIATE

3-year grant-funded appointment within individual groups

RESEARCH ASSOCIATE/FELLOW

Postdoctoral Fellow within individual groups, appointed by group leader

RESEARCH ASSISTANT

Postgraduate within individual groups, mainly grant-funded

GRADUATE STUDENT

3 or 4 year studentship within individual groups, mainly grant-funded

RESEARCH TECHNICIAN

Within individual groups, mainly grant-funded

LABORATORY ASSISTANT / TECHNICIAN

Within individual groups or part of core support, grant-funded

ITALICS: LEAVERS DURING THE LAST YEAR

POSTGRADUATE OPPORTUNITIES

As part of the University of Cambridge, the Institute welcomes enquiries from prospective graduate students. We have a thriving population of graduates who contribute greatly, not only to the stimulating research environment, but also to the life of the Institute as a whole. Additionally, graduates become members of the biological or medical sciences department to which their group is affiliated. Graduate studentships are supported mainly by the Wellcome Trust or Cancer Research UK but additional sponsorship may be solicited from a variety of sources, including government research councils. Applicants should write, in the first instance, to the leader of the group they wish to join.

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Director, Company of Biologists
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Academic Visitor (Professor of Theoretical Condensed
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Sabbatical Visitor (Max Perutz Professor of Molecular
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TRACY MITCHELL



ZEST CATERING

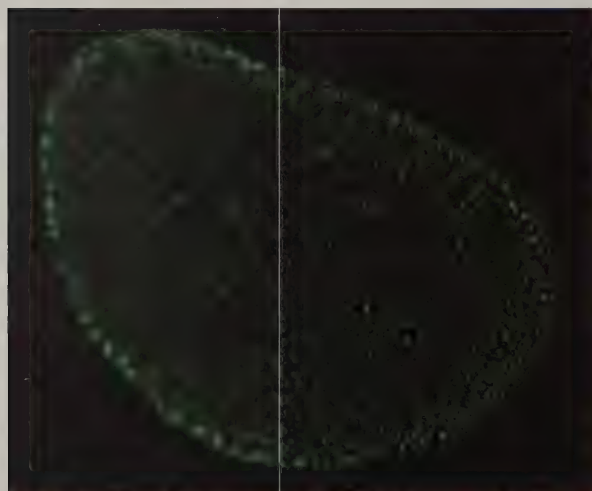
AMANDA HARRIS

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The following is a list of articles by members of the Institute that were either published or accepted for publication, since the date of publication of the last Annual Report.

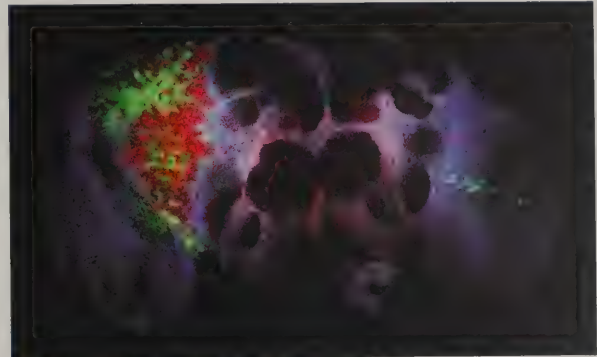
- 1 Ajduk A, Ilozie T, Windsor S, Yu Y, Seres KB, Bomphey RJ, Tom BD, Swann K, Thomas A, Graham C and **Zernicka-Goetz M** (2011) Rhythmic actomyosin-driven contractions induced by sperm entry predict mammalian embryo viability. **Nat Commun** 2, 417
- 2 Akhtar A, Fuchs E, Mitchison T, Shaw RJ, **St Johnston D**, Strasser A, Taylor S, Walczak C and Zerial M (2011) A decade of molecular cell biology: achievements and challenges. **Nat Rev Mol Cell Biol** 12, 669-674
- 3 Bannister AJ and **Kouzarides T** (2011) Regulation of chromatin by histone modifications. **Cell Res** 21, 381-395
- 4 Bartke T and **Kouzarides T** (2011) Decoding the chromatin modification landscape. **Cell Cycle** 10, 182
- 5 Bastock R and **St Johnston D** (2011) Oogenesis: matrix revolutions. **Curr Biology** 21, R231-R233
- 6 Belaya K and **St Johnston D** (2011) Using the mRNA-MS2/MS2CP-FP system to study mRNA transport during *Drosophila* oogenesis. **Methods Mol Biol** 714, 265-283
- 7 Blasius M, Forment JV, Thakkar N, Wagner SA, Choudhary C and **Jackson SP** (2011) A phospho-proteomic screen identifies substrates of the checkpoint kinase Chk1. **Genome Biol** 12, R78
- 8 Bonadies N, Foster SD, Chan WJ, Kvinlaug BT, Spensberger D, Dawson MA, Spooner E, Whetton AD, Bannister AJ, Huntly BJ and Gattgens B (2011) Genome-wide analysis of transcriptional reprogramming in mouse models of acute myeloid leukaemia. **PLoS One** 6, e16330 [Kouzarides Group]
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Visualisation of the nuclear pore complex (NPC) in HeLa cells using confocal microscopy (left) and with Stimulated Emission Depletion microscopy (STED), right. (Abderrahmane Kaidi, Jackson Group, 2011)

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Adult *Drosophila* brain with tumour. The tumour results from mutating a novel tumour suppressor during larval stages. Deadpan (a neural stem cell marker) is shown in red. Elav (neuronal marker) is shown in blue. (Tony Southall; Brand Group, 2011)

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JANUARY

ANDY BANNISTER: Domainex, Cambridge, UK

ANDREA BRAND: Centre for Biological Sciences, TIFR Bangalore, India

PHILIPPE COLLIN: Paris (Orsay-Ville), Institut Curie, Orsay, Paris, France

BORIS EGGER: University BEFRI, Leysin, Switzerland

JOSEP FORMENT: UK Genome Stability Network, Robinson College, Cambridge,

JOHN GURDON: Science Society, Wolfson College, Cambridge

STEVE JACKSON: Keystone Symposium on Genetic Instability, Colorado, USA

RICK LIVESEY: Cambridge Stem Cell Initiative Seminar, CIMR, Cambridge

ERIC MISKA: TAU microRNA Consortium, Tel Aviv, Israel; University of Oxford, Oxford

EMMA RAWLINS: ECCPS Mini-Symposium MPI Bad Nauheim and University of Giessen, Germany

AZIM SURANI: Keystone Symposium, Utah, USA; Keystone Symposium, New Mexico, USA

EMMANELLE VIRÉ: Université Paris Diderot Paris, France

MAGDALENA ZERNICKA-GOETZ: Stanford Stem Cell Institute, USA



C. elegans wild-type embryo stained for SPD-1 (green), tubulin (red) and DNA (blue). At anaphase, SPD-1 accumulates to the central spindle. (Kian-Yong Lee, Mishima Group, 2011)

FEBRUARY

JULIE AHRINGER: Astra Zeneca Seminar, Manchester University

ANDY BANNISTER: Domainex, Cambridge

TILL BARTKE: Friedrich-Miescher Institute, Basel, Switzerland; CRUK London Research Institute, Clare Hall, London

ANDREA BRAND: MRC Centre for Regenerative Medicine, University of Edinburgh, Edinburgh



OMX imaging of *S. pombe* microtubule organising motor protein (green) and cytoskeletal microtubules (red). Cell outlines are visualised using transmitted light (blue). (Jonathan Lawson, Carazo Salas Group, 2011)

STEVE JACKSON: Department of Biochemistry, Queens' College, University of Oxford

TONY KOUZARIDES: Epigenetics in Development & Disease, Miami, USA; Institute for Stem Cell Research, University of Edinburgh

RICK LIVESEY: Institute for Child Health, Great Ormond Street, London; WT Cambridge Stem Cell Initiative Retreat, Hinxton, Cambridge; Department of Neurology, Addenbrooke's Hospital, Cambridge

ERIC MISKA: EMBL/CIBB, Grenoble, France

EMMA RAWLINS: WT Cambridge Stem Cell Initiative Retreat, Hinxton, Cambridge; Division of Asthma, Allergy & Lung Biology, Kings College London

MARCH

JULIE AHRINGER: German Society for Cell Biology 34th Annual Meeting, Bonn, Germany

ANDY BANNISTER: Cellzome, Cambridge

TILL BARTKE: The Beatson Institute for Cancer Research, Glasgow

DELPHINE COUGOT: Department of Plant Sciences, University of Cambridge, Cambridge

JAMES DODGSON: British Yeast Group Meeting, Brighton

THOMAS DOWN: Institut Curie, Paris, France; European Bioinformatics Institute, Hinxton, Cambridge; Epigenetics and Developmental Programming Conference, Newcastle

STEVE JACKSON: Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER) Spain; 50th Anniversary Meeting of the American Society of Toxicology, Washington, USA

TONY KOUZARIDES: Institute for Stem Cell Research, Edinburgh; Frontiers in Biology Symposium, CRG-Barcelona, Barcelona, Spain

RICK LIVESEY: Cambridge Spring School in Neurogenerative Disease, Cambridge

ERIC MISKA: Science Foundation Ireland, Trinity College, Dublin, Ireland; University of Lyon, France

ALEX SOSSICK: EMBO Optical Microscopy Course 2011, Plymouth

DANIEL ST JOHNSTON: Frontiers in Biology Symposium, CRG-Barcelona, Barcelona, Spain; Patterson Institute for Cancer Research, Manchester

AZIM SURANI: North American Testis Workshop, Montreal, Canada; Institut Curie, Paris, France

SILVIA VIVARELLI: National Institute for Medical Research, London

LAURA WAGSTAFF: National Institute for Medical Research, London

BLERTA XHEMALCE: UMR7216 Epigenetics and Cell Fate Institute, Paris, France

PHIL ZEGERMAN: Cancer Research UK, LRI Retreat, Oxford; British Yeast Group Meeting - British Society for Cell Biology Prize Lecture, Brighton

APRIL

JULIE AHRINGER: Abcam, Non-Coding RNA, Epigenetic Memory and the Environment Conference, RIBA, London

ALYSON ASHE: Abcam Non-Coding RNA Epigenetic Memory and the Environment Conference, London

TILL BARTKE: Max Delbrück Center for Molecular Medicine, Berlin, Germany

THOMAS DOWN: Science BarCamp, Cambridge

JOSEP FORMENT: CABIMER, Sevilla, Spain

JOHN GURDON: American Associations of Anatomists, Washington DC, USA; University of Massachusetts, Massachusetts, USA; 6th Annual Wisconsin Stem Cell Symposium, Madison USA

STEVE JACKSON: Responses to DNA damage: from molecular mechanism to human disease, Egmond aan Zee, The Netherlands

TONY KOUZARIDES: Center for Integrative Genomics, University of Lausanne, Switzerland; Department of Cell Biology, University of Geneva, Switzerland

RICK LIVESEY: University of Trieste, Neuroscience Seminar, Italy; British Society for Developmental Biology & British Society for Cell Biology Joint Spring Meeting, University of Kent, Canterbury; Wiring the Brain Conference, Co Wicklow, Ireland; British Neuroscience Association Annual Meeting, Harrogate, Yorkshire

JOERG MANSFELD: 6th UK-Japan Cell Cycle Workshop, Windermere, Cumbria

MASANORI MISHIMA: 6th UK-Japan Cell Cycle Workshop, Windermere, Cumbria

ERIC MISKA: Abcam Non-Coding RNA, Epigenetic Memory and the Environment Conference, London; Keystone Symposium, Colorado, USA

EUGENIA PIDDINI: 52nd Annual *Drosophila* Research Conference, San Diego, USA

JON PINES: PhD Symposium, University of Helsinki, Finland

EMMA RAWLINS: Universities of Giessen and Marburg Lung Center Regeneration Symposium, MPI Bad Nauheim and University of Giessen, Germany

MAGDALENA ZERNICKA-GOETZ: Stem Cell Institute, California Institute of Technology, USA

MAY

RAFAEL CARAZO-SALAS: Cambridge Institute for Medical Research, Cambridge

JOHN GURDON: Young Embryologists, King's College, London

STEVE JACKSON: Max Planck Institute, Germany; Liverpool Cancer Research Annual Meeting, Liverpool

TONY KOUZARIDES: CRG - Barcelona, Spain; Institute Pasteur, Paris France

RICK LIVESEY: Neuroscience and Mental Health Institute, University of Cardiff; Harvard Stem Cell Institute, USA

ERIC MISKA: MRC Prion Unit, London; IMBA, Vienna, Austria; University of Utrecht; EMBO Practical Course on Micro-RNA Profiling, National University of Ireland, Galway

JON PINES: Biocentrum, University of Basel, Switzerland; Doctoral School Symposium, University of Tartu and Konstanz, Estonia

AZIM SURANI: Wellcome Trust Sanger Institute, Cambridge

EMMANELLE VIRÉ: School of Biological Sciences, University of Portsmouth, UK

LAURA WAGSTAFF: Department of Zoology, University of Cambridge, Cambridge

JULIE WOOLFORD: Cambridge Research Institute, Cambridge

MAGDALENA ZERNICKA-GOETZ: Stem Cell and Regenerative Biology, Harvard, USA

JUNE

PAOLO AMARAL: XI Genetics Workshop, Institute of Biosciences, UNESP, São Paulo, Brazil

RAFAEL CARAZO SALAS: MRC Laboratory for Molecular Cell Biology & Cell Biology Unit, London

JOHN GURDON: University of Cambridge; ISSCR Annual Meeting, Toronto, Canada

STEVE JACKSON: School of Biological Sciences, University of Edinburgh; Cambridge Cancer Centre Symposium, Cambridge; University of Copenhagen, Denmark

RICK LIVESEY: Department of Physiology, Anatomy and Genetics Seminar Series, University of Oxford

MASANORI MISHIMA: University of San Diego, USA

ERIC MISKA: International *C. elegans* Meeting, Los Angeles, USA; Russ Fernald Lab, Stanford University, USA

JON PINES: Global Centre of Excellence Program, Tokyo Institute of Technology, Japan; MEXT Priority Research Project Hakone, Japan

DANIEL ST JOHNSTON: Wellcome Trust Sanger Institute, Cambridge

ALEX SAPETSCHNIG: International *C. elegans* Meeting, Genetics Society of America, Los Angeles, USA

AZIM SURANI: ISSCR Annual Meeting, Toronto, Canada

EMMANELLE VIRÉ: Laboratoire de Biochimie, Faculté de Médecine, Université d'Auvergne, France

JULIE WATSON: EuroSyStem Consortium, Prague, Czech Republic; U3A Cambridge Group, Cambridge

JULY

JULIE AHRINGER: 70th Annual Meeting of the Society for Developmental Biology, Chicago, USA;

MELANIE BLASIUS: Genetic Toxicology, Gordon Research Conferences, Barga, Italy

TILL BARTKE: Institute of Molecular Biology, Mainz, Germany

ANDREA BRAND: 70th Annual Meeting of the Society for Developmental Biology, Chicago, USA

RAFAEL CARAZO SALAS: EMBL, Heidelberg, Germany

THOMAS DOWN: Advances in Medical Genomics, QMUL, London; BOSC, Vienna, Austria

JOHN GURDON: Cambridge University Science Summer School, University of Cambridge

RICK LIVESEY: Institute of Neurology, London; Science Summer School, University of Cambridge; The Belgian Society for Cell and Developmental Biology, Summer Meeting, Rochehaut, Belgium

ERIC MISKA: MRC Clinical Centre, London; Sanger EBI, Hinxton, Cambridge; EMBO YIP Meeting, Heidelberg, Germany; Biochemical Society, Cambridge

EMMA RAWLINS: Stem Cells and Cell Therapies in Lung Biology and Lung Diseases, University of Vermont College of Medicine, USA

AZIM SURANI: Wellcome Trust Centre for Stem Cell Research, Cambridge; University of Oxford, Oxford

SILVIA VIVARELLI: National Institute for Medical Research, London

LAURA WAGSTAFF: National Institute for Medical Research, London

MAGDALENA ZERNICKA-GOETZ: European Society of Human Reproduction and Embryology Meeting, Barga, Italy

AUGUST

ANDREA BRAND: School of Biological Sciences, University of Sydney, Australia

STEVE JACKSON: Biochemical Society, Hinxton, Cambridge

NIMESH JOSEPH: Sphere Fluidics Talk, Cambridge

TONY KOUZARIDES: FASEB Summer Research Conferences, Snowmass, Colorado, USA

MAGDALENA ZERNICKA-GOETZ: EMBO Intracellular RNA Localization and Localized Translation, Barga, Italy

SEPTEMBER

JULIE AHRINGER: European Science Foundation: From Phenotypes to Pathways, Cambridge; EMBO Nuclear Structure and Dynamics, Isle sur la Sorgue, France,

PAOLO AMARAL: Computational Biology Seminar Series, Institute for Molecular Bioscience, University of Queensland, Brisbane, Australia

ANDREA BRAND: Cambridge Neural Stem Cell Symposium, St Johns College, Cambridge; Howard Hughes Medical Institute, Ashburn Virginia, US; Cold Spring Harbor Laboratory Stem Cell Biology Meeting, Cold Spring Harbor, New York USA; SKMB Gene Regulation Workshop, Center for Integrative Genomics, Lausanne, Switzerland

RAFAEL CARAZO SALAS: 8th Bertinoro Computational Biology Meeting, Bertinoro, Italy; Physics of Living Matter Meeting, CMS, Cambridge

VINCENT GAGGIOLI: Cold Spring Harbor Laboratory Eukaryotic DNA Replication and Genome Maintenance, Cold Spring Harbour, New York, USA

JOHN GURDON: Athens Academy, Athens, Greece; Anne McLaren Laboratory for Regenerative Medicine, Leckhampton House, Cambridge; St Mary's School College, Ascot, Kent

STEVE JACKSON: EMBO-EMBL, Greece

TONY KOUZARIDES: Justus-Liebig-Universität Giessen, Germany

RICK LIVESEY: Wellcome/MRC Neurodegeneration Initiative Annual Meeting, Edinburgh; Cambridge Neural Stem Cell Symposium, St Johns College, Cambridge

JON PINES: University of Utrecht, The Netherlands; Paterson Institute Manchester; Norwegian Cancer Symposium, Oslo, Norway

EMMA RAWLINS: Cambridge Stem Cell Initiative Seminar, Cambridge Institute for Medical Research, Cambridge

DANIEL ST JOHNSTON: ERDC Conference, Lisbon, Portugal

ALEX SOSSICK: Friedrich-Miescher Institute for Biomedical Research, Basel, Switzerland

AZIM SURANI: Max Delbrück Center for Molecular Medicine, Berlin, Germany

PHIL ZEGERMAN: Cold Spring Harbor Laboratory Eukaryotic DNA Replication and Genome Maintenance, Cold Spring Harbour, New York, USA



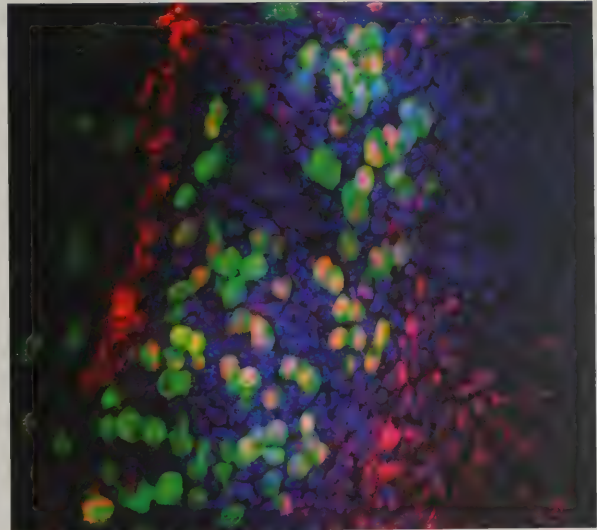
Follicle cell clones (Dmitry Nashchekin, St Johnston Group, 2011)

OCTOBER

- JUAN FRANCISCO ABENZA MARTINEZ:** Nanoday Conference, Newnham College, Cambridge
- JULIE AHRINGER:** Max Planck Institute for Molecular Genetics, Berlin, Germany
- ANDY BANNISTER:** Domainex, Cambridge
- RAFAEL CARAZO SALAS:** Cancer Research UK, London
- MARK DAWSON:** Cambridge Haematopoiesis Seminar Series, Cambridge Institute for Medical Research, Cambridge
- JENNY GALLOP:** Department of Biochemistry, University of Oxford; EMBO-FEBS Lecture Course/European Cytoskeletal Forum Meeting, Stresa, Italy
- VERONIKA GRAML:** First International System X.ch Conferences on Systems Biology, Basel, Switzerland
- JOHN GURDON:** EMBO Workshop, IGBMS Strasbourg, France
- STEVE JACKSON:** Queens University, Belfast; 39th Annual Meeting, Frontiers in Cell Biology, Copenhagen, Denmark; Babraham Institute, Cambridge; 5th Chemical Biology and Molecular Medicine Symposium, CRI, Cambridge
- TONY KOUZARIDES:** Cellzone/CellCentric/BioFocus, Chesterford Research Park, Chesterford; MRC Clinical Sciences Centre, London
- RICK LIVESEY:** Takeda UK Ltd, Cambridge
- JOERG MANSFELD:** Centre for Protein Research, Copenhagen, Denmark
- JON PINES:** Institute for Research in Immunology and Cancer, Montreal, Canada; 5th International Workshop on Cell Regulation in Division and Arrest, Okinawa, Japan
- DANIEL ST JOHNSTON:** Institut Curie, Paris, France

NOVEMBER

- PAOLO AMARAL:** London Chromatin Club, University College London
- ANATOLE CHESSEL:** OMX Users' Meeting, Paris, France; Cancer Research UK, London Research Institute, London
- MARK DAWSON:** Australian Centre for Blood Diseases, Melbourne, Australia; Peter MacCullum Cancer Institute, Melbourne, Australia
- JENNY GALLOP:** Cambridge Cell Biology Seminar; CIMR, Cambridge; Department of Biochemistry, University of Bristol
- JOHN GURDON:** Academy of Medical Sciences Honorary Fellowship, London; Cardiff Scientific Society Cardiff, Wales; MRC/NIMR Mill Hill, London
- STEVE JACKSON:** Universidad Internacional de Andalucia, Baeza, Spain; Health Research Board, Science Foundation Ireland and Molecular Medicine, Dublin, Ireland
- RICK LIVESEY:** Department of Cell and Developmental Biology, University College, London
- ERIC MISKA:** CSHL *C elegans* Course Organiser, Cold Spring Harbour, New York, USA; University of Wisconsin, Madison, USA
- JON PINES:** Cell Polarity in Health and Disease Workshop, Ottawa, Canada
- DANIEL ST JOHNSTON:** Cell Polarity in Health and Disease Workshop, Ludwig Institute for Cancer Research, Oxford



Primordial germ cells in a mouse gonad at e11.5". In blue is DAPI, green is GOF reporter, red is Histone H3 Lysine 27 trimethylation (H3K27me3). This is a whole mount staining. (Roopsha Sengupta, Surani Group, 2011)

- AZIM SURANI:** CNIO (Spanish National Cancer Centre) Conference, Madrid, Spain; Royal Society, London; Wellcome Trust, Hinxton, Cambridge
- MAGDALENA ZERNICKA-GOETZ:** Institute of Reproductive Science, Oxford; Cell Polarity in Health and Disease Workshop, Ludwig Institute for Cancer Research, Oxford

DECEMBER

- JUAN FRANCISCO ABENZA MARTINEZ:** Institut Curie, Paris, France
- ANDREA BRAND:** Rosalind Franklin Society, Washington DC, USA
- MARK DAWSON:** American Society of Haematology Annual Meeting, San Diego, USA
- JENNY GALLOP:** Tissue Systems Seminar Series, University of Manchester, Manchester
- JOHN GURDON:** Charterhouse School, Godalming; Cell Symposia: Stem Cell Programming and Reprogramming, Lisbon, Portugal
- STEVE JACKSON:** Genes and Cancer Symposium, Warwick
- TONY KOUZARIDES:** University of Leeds, Leeds; Abcam Chromatin: Structure and Function 2011, Aruba
- JON PINES:** Nordic Mitotic Network Meeting, Copenhagen, Denmark
- AZIM SURANI:** BIOTEC (Biotechnology Centre) Dresden, Germany

STAFF AFFILIATIONS

JULIE AHRINGER is a member of the MRC Career Development Panel and a member of the Scientific Advisory Board of Reactome.

ANDREA BRAND is a Founding Board Member of The Rosalind Franklin Society (USA), member of Sectional Committee 7 of the Royal Society, member of the Royal Society Research Appointment Panel B, member of the EMBO Young Investigator Committee, member of the Review Panel of the Developmental Biology Unit, EMBL (Heidelberg, Germany) and external advisor to the Management Board of the National Centre for Biological Sciences (Bangalore, India). She is also a member of the steering group of the Cambridge Women in Science, Engineering and Technology Initiative, Patron of the Cambridge Science Festival, and member of Council, Jesus College.

JOHN GURDON is an honorary member of the Scientific Advisory Board of the Harvard Stem Cell Institute (USA) and the Rambam Medical Center (Israel), an honorary member of the British and American Anatomical Societies, Chairman of the Company of Biologists, a board member of Diagnostics for the Real World and a member of the Faculty of 1,000.

STEVE JACKSON is founding Scientist and Chief Scientific Officer of MISSION Therapeutics Ltd. He is also Chairman of the Board of the Scottish Centre for Cell Signalling (SCILLS), a member of the Cancer Research UK Drug Discovery Advisory Group, the Strategic Board of the Drug Discovery Program (IFOM-IEO, Milan, Italy), the Radiation Oncology and Biology External Advisory Board and the Scientific Advisory Board for the Beatson Institute. He is on the Steering Committee for the Cambridge Cancer Centre, and selection committee for Carcinogenesis Integrative Cancer Research Awards.

TONY KOUZARIDES is a member of the Cancer Research UK Science and Strategy Advisory Group, part of the Scientific Advisory Board for the Centre for Genomic Research (Spain), the Institute of Molecular Biology (Crete) and the Centre for Epigenetics and Biology (Spain). He is the founder and director of a Spanish cancer charity Vencer el Cancer (Conquer Cancer) and a founder of Chroma Therapeutics and Abcam Plc. He is a Director of Abcam Plc and on the Scientific Advisory Board of Glaxo Smith Kline and Cellzome.

JONATHAN PINES is a member of the Cancer Research UK Fellowship Committee, and a member of the Scientific Advisory Boards for the Institute of Biology, Paris Seine, and the Institute of Biochemistry, ETH, Zurich.

DANIEL ST JOHNSTON is a Director of the Wellcome Trust Four-Year PhD programme in Developmental Biology at the University of Cambridge, and is a non-executive Director of the Company of Biologists.

AZIM SURANI is Chairman of the Scientific Advisory Board of the Centre for Trophoblast Research, University of Cambridge; Member of the Steering Committee of the Cambridge Stem Cell Initiative, and Leader of the Pluripotency Programme; Member of the Cambridge India Partnership Advisory Group; Founder and Chief Scientific Advisor for CellCentric Ltd; Member of the Steering Committee for the UK Stem Cell Bank; Member of the Royal Society Nominations Committee; Visiting Professor, University of Kyoto, Japan.

MAGDALENA ZERNICKA-GOETZ is a Stanley Elmore Senior Research Fellow at Sidney Sussex College and Board Member of the Cambridge Philosophical Society.

HONOURS AND AWARDS

STEVE JACKSON – Royal Society Buchanan Medal

PHIL ZEGERMAN – Cancer Research UK Hardiman Redon prize 2010

AZIM SURANI – Extraordinary Fellow, King's College, Cambridge

EDITORIAL BOARDS OF JOURNALS

JULIE AHRINGER – Public Library of Science Biology, Molecular Systems Biology

ANDREA BRAND – Neural Development, Fly, Biology Image Library

JOHN GURDON – Current Biology, Development, Growth and Differentiation, International Journal of Developmental Biology, Proceedings of the National Academy of Sciences of the USA

STEVE JACKSON – Carcinogenesis, EMBO Journal, DNA Repair, Ageing, Genes and Development, Current Biology.

RICK LIVESEY – BMC Developmental Biology, Molecular Autism

EMMA RAWLINS – Pediatric Research

JON PINES – EMBO Journal, EMBO Reports

DANIEL ST JOHNSTON – Development, Faculty of 1,000

AZIM SURANI – Cell, Nature Communications, Cell Stem Cell, BMC Epigenetics and Chromatin, Epigenome, Epigenomics, Epigenetic Regulators, Regenerative Medicine, Differentiation, Stem Cell Research and Therapy, Faculty of 1,000

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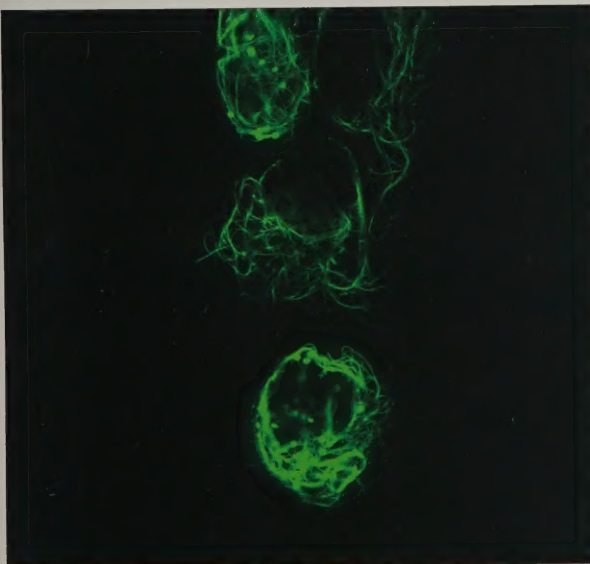
PAULINA KOLASINSKA-ZWIERZ: Completed PhD and left in 2010 (Ahringer Group)

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JING SU: Postdoctoral Researcher, Microarray group, EBI, Cambridge, UK (Collaborating PhD student Down Group)



GFP-RNF36 (Ring Finger 36 protein) live imaging in U2OS cells. RNF36 is an Ubiquitin E3-ligase. (Yaron Galanty, Jackson Group, 2011)

DESTINATIONS OF LEAVERS DURING 2011

ROY (TANG YI) TEO: Returned to Singapore to complete his A*STAR PhD course (Zernicka-Goetz Group)

URUPORN THAMMONGKOL: Left to work in business in Thailand (Livesey Group)

ALYSON THOMPSON: Bain & Co, London, UK (Brand Group)

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JUTTA WELLMAN: Deceased (Brown Group)

LUCY WHEATLEY: Field Application Specialist, Promega (St Johnston Group)

PAO-SHU (PAUL) WU: Clinical Resident, Department of Pathology, Taipei Veterans General Hospital, Taipei, Taiwan (Brand Group)

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SKY FEUER: PhD student, UCSF, San Francisco, USA (Ahringer Group)

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MARTIN BINDER: Part III Maths student, University of Cambridge (Livesey Group)

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KAI LUDWIG: (Visiting student) Undergraduate student, University of Wisconsin-Madison, USA (Miska Group)

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MATT NEWTON: (Volunteer researcher) Completing A-Levels (Brown group)

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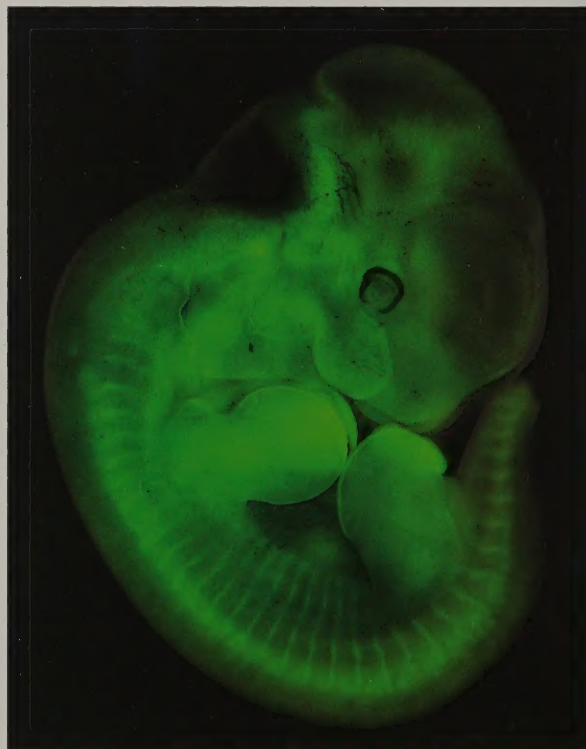
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ELIANA TACCONI: (Volunteer researcher) PhD student, Gray Institute for Radiation Oncology and Biology, University of Oxford, UK (Pines group)



Mouse embryo expressing GFP (Samantha Morris, Zernicka-Goetz Group, 2011)



Professor Sir John Gurdon investigates one of science's great unanswered questions: what does it actually *feel* like to be a frog? Hoppity-hop.... (photo by John Overton)

ACKNOWLEDGEMENTS

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Front cover: Super-resolution image of developing dendritic spines in human iPS derived cortical neurons. Green DiO, Blue DAPI. (Peter Kirwan, Livesey Group, 2011)

Back cover: Institute retreat, photos by Peter Williamson and John Overton.



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